Fibrose et insuffisance cardiaque

Romain Eschalier

N°

UNIVERSITE D'AUVERGNE

ECOLE DOCTORALE SCIENCES DE LA VIE, DE LA SANTE, DE L'AGRONOMIE ET DE L'ENVIRONNEMENT

THESE pour l'obtention du

DOCTORAT de l'Université d'Auvergne

PAR

ESCHALIER Romain

né le 12 Mai 1981 à Clermont-Ferrand

Présentée et soutenue publiquement le 04 Octobre 2013

FIBROSE

ET

INSUFFISANCE CARDIAQUE

Président: Monsieur CITRON Bernard, Professeur, Clermont-Ferrand

Membres du jury:

- **Rapporteurs**
  - Monsieur DESNOS Michel, Professeur, Paris
  - Monsieur LOGEART Damien, Professeur, Paris
- **Co-directeurs**
  - Monsieur LUSSON Jean-René, Professeur, Clermont-Ferrand
  - Monsieur ROSSIGNOL Patrick, Professeur, Nancy
  - Monsieur ZANNAD Faïez, Professeur, Nancy
- Monsieur MOTREFF Pascal, Professeur, Clermont-Ferrand

Ce travail a été réalisé en co-direction entre les équipes CIC-P 9501 du CHU de Nancy et l'UMR6284 ISIT/Cavity CNRS, Clermont-Ferrand.

N°

UNIVERSITE D'AUVERGNE

ECOLE DOCTORALE SCIENCES DE LA VIE, DE LA SANTE, DE L'AGRONOMIE ET DE L'ENVIRONNEMENT

THESE pour l'obtention du

DOCTORAT de l'Université d'Auvergne

PAR

ESCHALIER Romain

né le 12 Mai 1981 à Clermont-Ferrand

Présentée et soutenue publiquement le 04 Octobre 2013

FIBROSE ET INSUFFISANCE CARDIAQUE

Président: Monsieur CITRON Bernard, Professeur, Clermont-Ferrand

Membres du jury:

- **Rapporteurs**
  - Monsieur DESNOS Michel, Professeur, Paris
  - Monsieur LOGEART Damien, Professeur, Paris
- **Co-directeurs**
  - Monsieur LUSSON Jean-René, Professeur, Clermont-Ferrand
  - Monsieur ROSSIGNOL Patrick, Professeur, Nancy
  - Monsieur ZANNAD Faïez, Professeur, Nancy
- Monsieur MOTREFF Pascal, Professeur, Clermont-Ferrand

REMERCIEMENTS

Aux Professeurs Zannad et Rossignol :

Je tiens à vous exprimer mon profond respect et vous remercier de m'avoir accueilli, d'avoir dirigé ce travail et de m'avoir intégré dans cette famille du CIC de Nancy. Merci de m'avoir enseigné les exigences, et les plaisirs de la recherche clinique avec un sens critique et une rigueur indispensables. Je serai heureux de poursuivre avec vous comme déjà évoqué d'autres travaux de recherche.

Aux Professeurs Desnos et Logeart:

Je souhaite vous adresser mes plus sincères et respectueux remerciements pour m'avoir fait l'honneur d'accepter de juger ce travail.

Au Professeur Lusson:

Je tiens à vous remercier de votre soutien et de votre confiance. Soyez assuré de mon plus profond respect. Merci de votre accueil me confortant dans ma volonté de me lancer dans cette spécialité, de votre enseignement clinique et de nos échanges lors de nos staffs ou de nos entretiens comme celui de la place Stanislas.

Au Professeur Citron :

Je souhaite vous remercier de m'avoir fait l'honneur d'accepter de présider ce jury mais également de m'avoir accueilli et pour votre confiance lors de la création de notre pôle.

Au Professeur Motreff:

Cher Pascal, Merci pour ton enseignement et ta confiance, mais également d'avoir accepté de faire partie de ce jury. Je suis heureux et honoré de pouvoir continuer à travailler avec toi dans le service.

Je souhaite remercier amicalement les Pr P.Y. Marie et V. Sapin et les Dr A. Kearney-Schwartz, R. Fay et F. Pinet pour leur accompagnement dans la réalisation scientifique, technique et statistique de ces travaux, mais surtout pour toutes ces discussions et rencontres très enrichissantes.

Je souhaite également remercier chaleureusement l'équipe du CIC-Plurithématique 9501 de Nancy et l'ensemble de l'équipe de Cardiologie de Clermont-Ferrand qui m'ont permis de toujours me sentir à ma place. Un certain nombre d'entre vous sont devenus bien plus que des collègues!

PRODUCTIONS SCIENTIFIQUES

- **PUBLICATIONS**

1/ Mandry D, **Eschalier R**, Kearney-Schwartz A, Rossignol P, Joly L, Djaballah W, Bôhme P, Escanyé JM, Vuissoz PA, Fay R, Zannad F, Marie PY. *Comprehensive MRI analysis of early cardiac and vascular remodeling in middle-aged patients with abdominal obesity.* J Hypertens. 2012 Mar;30(3):567-73.

2/ **Eschalier R**, Jean F, Pereira B, Monzy S, Vorilhon C Mactoux V, Citron B, Sapin V, Motreff P, Lusson JR. *Is there benefit in optimising heart failure treatment in over-80 year-old patients? (HF-80 study): study protocol for a randomized controlled trial.* Trials. 2012 Mar 6;13(1):25.

3/ **Eschalier R**, McMurray JJV, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F, Pitt B. *Safety and efficacy of eplerenone in patients at high risk for hyperkalemia and/or worsening renal function: Analyses of EMPHASIS-HF study subgroups.* J Am Coll Cardiol (2013).

4/ **Eschalier R**, Fertin M, Fay R, Bauters C, Zannad F, Pinet F and Rossignol P. *Extracellular matrix turnover biomarkers predict long term left ventricular remodeling after myocardial infarction (insights from the REVE-2 study)*. Circ Heart Fail, 2013. article in press.

- **COMMUNICATIONS ORALES**

1/ **Eschalier R**, Rossignol P, Kearney-Schwartz A, Adamopoulos C, Karatzidou K, Fay R, Mandry D, Marie PY, Zannad F. *Rénine : une nouvelle cible thérapeutique dans le remodelage cardiaque des sujets présentant une obésité abdominale.* Journée de la recherche de l'IFR Santé Auvergne et de l'Université d'Auvergne. ***25 Novembre 2010, Clermont-Ferrand.***

2/ **Eschalier R**, Rossignol P, Kearney-Schwartz A, Adamopoulos C, Karatzidou K, Fay R, Mandry D, Marie PY, Zannad F. *Neurohormonal determinants of early changes in cardiovascular changes in structure and function in subjects with abdominal obesity.* Journées Européennes de la Société Française de Cardiologie 2012 ***(JESFC),_12 Janvier 2012, Paris.***

3/ **Eschalier R**, Rossignol P, Kearney-Schwartz A, Adamopoulos C, Karatzidou K, Fay R, Mandry D, Marie PY, Zannad F. *Neurohormonal determinants of early changes in cardiovascular changes in structure and function in subjects with abdominal obesity.* ***24 Janvier 2012, MEDIA meeting, Leiden.***

- **COMMUNICATIONS AFFICHEES**

1/ **Eschalier R**, Rossignol P, Kearney-Schwartz A, Adamopoulos C, Karatzidou K, Fay R, Mandry D, Marie PY, Zannad F. *Neurohormonal determinants of early changes in cardiovascular changes in structure and function in subjects with abdominal obesity.* Congrès Pharmacologie, Physiologie et thérapeutique ***(P2T). 3-5 Avril 2012, Dijon.***

2/ **Eschalier R**, Rossignol P, Kearney-Schwartz A, Adamopoulos C, Karatzidou K, Fay R, Mandry D, Marie PY, Zannad F. *Neurohormonal determinants of early changes in cardiovascular changes in structure and function in subjects with abdominal obesity.* European Society of Cardiology Congress ***(ESC). 25-29 Août 2012, Munich.***

3/ **Eschalier R**, Fertin M, Fay R, Bauters C, Zannad F, Pinet F and Rossignol P. *Extracellular matrix turnover biomarkers predict long term left ventricular remodeling after myocardial infarction (insights from the REVE-2 study)*. European Society of Cardiology Congress ***(ESC). 31 Août – 4 Septembre 2013, Amsterdam.***

TABLE DES MATIÈRES

1 INTRODUCTION

L'insuffisance cardiaque (IC) chronique représente la pathologie cardiovasculaire d'avenir car son incidence et sa prévalence sont en pleine croissance par le vieillissement de la population, mais aussi par une meilleure prise en charge des cardiopathies ischémiques. L'IC constitue un enjeu de santé publique du fait de sa prévalence et de sa morbimortalité importantes mais également de son coût pour la société. Il apparaît donc nécessaire de traiter de façon optimale les patients atteints mais surtout de prévenir la survenue de cette pathologie dans différentes populations à risque de remodelage ventriculaire gauche et donc de développer une IC.

Ce travail de thèse avait pour objectif d'évaluer l'intérêt des peptides collagéniques sanguins, indicateurs de fibrose myocardique, dans différentes populations à haut risque de développer une insuffisance cardiaque (patients présentant une obésité abdominale ou en post-infarctus du myocarde) ou déjà symptomatiques (post-infarctus du myocarde). La fibrose participe à la rigidité artérielle et ventriculaire qui sont des éléments précurseurs de l'insuffisance cardiaque chez des patients asymptomatiques (comme les hypertendus) et qui favorisent également les troubles du rythme ventriculaires graves et l'insuffisance cardiaque terminale qui sont les deux principales causes de mortalité de l'insuffisance cardiaque. Il est donc nécessaire d'appréhender les mécanismes physiopathologiques de transition vers l'insuffisance cardiaque de pathologies en plein essor telles que l'obésité abdominale et l'infarctus du myocarde.

L'intérêt porté à la fibrose est légitimé par l'efficacité des thérapeutiques anti-fibrotiques (p.ex. antagonistes des récepteurs aux minéralocorticoïdes) chez des patients présentant une insuffisance cardiaque à fonction systolique altérée en post-infarctus ou aux différents stades de gravité.

Notre équipe a donc décidé de mener plusieurs études afin d'évaluer cette problématique :

- L'étude R2C2 : étude transversale ayant pour objectif d'évaluer l'existence éventuelle de modifications cardiaques et artérielles chez des patients asymptomatiques présentant une obésité abdominale sans autre facteur de risque cardiovasculaire.

- L'étude REVE-2 : en partenariat avec l'équipe Inserm U744 de l'institut Pasteur de Lille (F. Pinet, C. Bauters, M. Fertin), nous avons évalué chez des patients pris en charge pour infarctus du myocarde antérieur, l'intérêt des peptides collagéniques pour prédire le remodelage ventriculaire gauche à 1 an ou la morbi-mortalité à 3 ans.

- Une étude en sous-groupes d'EMPHASIS-HF : chez des patients à haut risque de morbi-mortalité et de remodelage, nous avons évalué la sécurité d'utilisation et l'efficacité d'un antagoniste des récepteurs aux minéralocorticoïdes, thérapeutique anti-fibrotique par excellence.

2 DONNÉES BIBLIOGRAPHIQUES: INSUFFISANCE CARDIAQUE, SITUATIONS À RISQUE, BIOMARQUEURS

2.1 INSUFFISANCE CARDIAQUE

2.1.1 *Définition*

L'insuffisance cardiaque (IC) chronique est un syndrome, d'apparition progressive, compliquant les différentes pathologies cardiaques. Plusieurs définitions de l'IC chronique existent[1,2], sans qu'aucune ne soit entièrement satisfaisante. Une définition simple de l'IC chronique est difficile car son diagnostic prend en compte non seulement la symptomatologie clinique mais également des données issues d'examens complémentaires (échocardiographie, angiocoronarographie, imagerie par résonance magnétique (IRM) cardiaque…).

La classification établie par la New York Heart Association[3,4] est actuellement la méthode de référence pour stratifier les patients atteints d'IC et suivre leur évolution. Celle-ci permet d'établir le degré d'IC chronique en fonction du niveau de dyspnée ressentie par le patient lors des efforts qu'il arrive à fournir. Elle est utilisée couramment aussi bien en pratique clinique quotidienne que dans les essais cliniques de l'IC malgré le fait qu'elle soit uniquement clinique et qu'elle ne permette pas d'appréhender la physiopathologie de l'IC.

La société européenne de Cardiologie[5] définit en 2012 l'IC comme « une anomalie de structure ou de fonction du myocarde conduisant à l'incapacité du cœur à assumer la délivrance de l'oxygène à des taux suffisants pour la consommation métabolique de base des tissus malgré des pressions de remplissage normales ». L'insuffisance cardiaque est enfin définie cliniquement comme un syndrome associant des symptômes typiques (p.ex.

dyspnée, asthénie) et des signes cliniques (p.ex. turgescence jugulaire, crépitants pulmonaires, déplacement du choc de pointe) témoignant d'anomalies de structure ou de fonction cardiaques.

L'American College of Cardiology (ACC) a également établi une classification en 2005 (cf. figure 1) basée sur les degrés de sévérité de l'IC chronique :

- *le stade A* correspond à un risque élevé de survenue d'IC chronique du fait de la présence de facteurs de risque cardiovasculaires mais sans anomalie cardiaque structurelle ni symptôme ;
- *le stade B* correspond à la présence d'une maladie cardiaque structurelle mais toujours asymptomatique ;
- *le stade C* à une atteinte cardiaque symptomatique ;
- *le stade D* à l'IC chronique dite réfractaire à toute thérapeutique[6].

Cette classification met l'accent sur les stades précoces de la maladie (A et B). Toutefois, les mécanismes de transition vers les stades symptomatiques sont encore à ce jour mal connus.

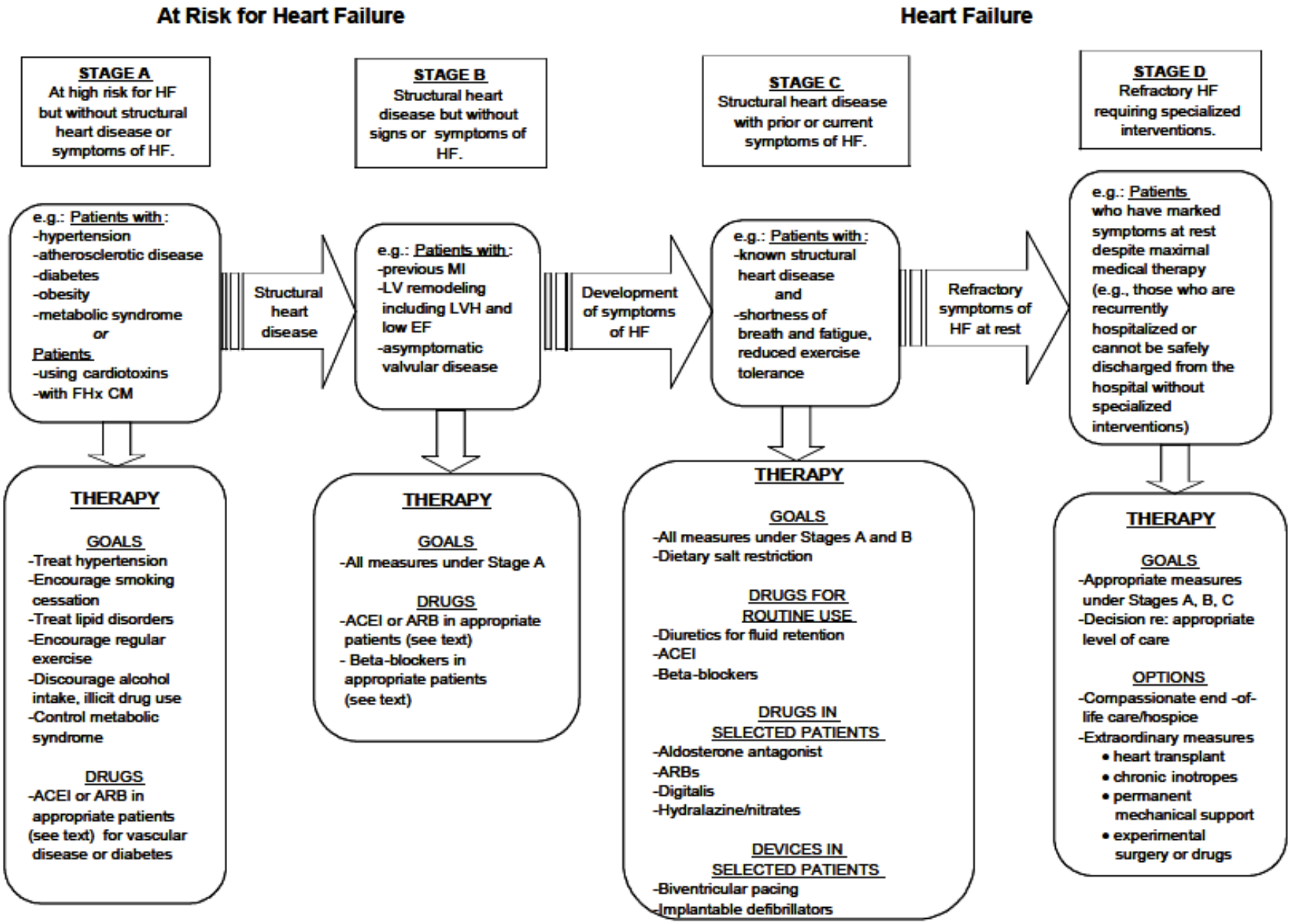


Figure 1. Stages in the development of heart failure/recommended therapy by stage. FHx CM indicates family history of cardiomyopathy; ACEI, angiotensin converting enzyme inhibitors; and ARB, angiotensin receptor blocker.

2.1.2 *Epidémiologie*

Les maladies cardiovasculaires ont été, jusqu'en 2004 la première cause de mortalité en France (INSEE). Elles restent encore la deuxième cause derrière les pathologies néoplasiques. L'insuffisance cardiaque chronique est actuellement la seule pathologie cardiovasculaire dont l'incidence et la prévalence sont en augmentation du fait du vieillissement de la population, mais aussi d'une meilleure prise en charge des différentes cardiopathies et notamment les cardiopathies ischémiques. La prévalence de l'IC est évaluée en Europe à 2 à 3 % de la population générale[7,8], à plus de 10% chez les plus de 70 ans et même plus de 20% au-delà de 80 ans[9]. On estime à 1 million le nombre de patients insuffisants cardiaques en France[10] soit une prévalence de 2,2%. Ils représentent 150 000 hospitalisations / an, pour un séjour moyen de 10,7 jours[11]. Il s'agit de la première cause d'hospitalisation dans notre pays.

L'étude de la cohorte Framingham apporte des renseignements complémentaires[12]: l'âge moyen du diagnostic d'IC est de 70 ans, l'incidence passe de 3‰ entre 50 et 59 ans, à 27‰ entre 80 et 89 ans chez l'homme. Cette cohorte montre que la survie à 5 ans, une fois le diagnostic d'IC chronique posé, est de 25% chez l'homme et de 38% chez la femme[12,13]. Le pronostic reste donc sombre. L'insuffisance cardiaque chronique est toujours une des premières causes de décès d'origine cardiovasculaire *[INSERM. Causes médicales de décès, année 1996, résultats définitifs. Service d'information sur les causes médicales de décès SC8.]*. La mortalité attribuable en France à l'IC chronique est estimée à environ 30 000 cas / an. La mortalité intra hospitalière de l'insuffisance cardiaque aiguë est supérieure à celle de l'infarctus du myocarde à 8,2% en 2009[14]. Il y a tout de même eu une amélioration du pronostic lors des vingt dernières années en Europe[15].

L'insuffisance cardiaque chronique dans les pays occidentaux est donc un problème majeur de santé publique. En France, on estime que les dépenses concernant l'IC chronique représentent environ 1.1 milliard d'euros, soit plus d'1% du total des dépenses de santé. Du fait du vieillissement de la population et de l'optimisation de la prise en charge des différentes cardiopathies, ces données risquent de s'aggraver. Les données de la CNAM

2008 récemment publiées confirment le vieillissement de cette population mais aussi la gravité de cette maladie (âge moyen de 77 ans, taux annuel de décès de 16,6%).

2.1.3 *Etiologies*

L'insuffisance cardiaque chronique représente l'évolution naturelle de la majorité des pathologies cardiaques. Les coronaropathies et l'hypertension artérielle (HTA) sont responsables de la majorité des cas d'IC chronique dans les pays occidentaux. La cardiopathie ischémique est responsable d'environ deux tiers des cas d'IC à fonction ventriculaire gauche altérée. Plus généralement, le syndrome métabolique (HTA, diabète, obésité, dyslipidémie) est la première cause d'IC chronique. La relation entre HTA, dyslipidémie ou diabète et l'IC chronique est bien documentée, au contraire de l'obésité.

Les différentes étiologies de l'IC ont évolué au cours du XXème siècle avec la prédominance actuelle et toujours en pleine expansion des causes ischémiques au dépend des cardiopathies valvulaires post-rhumatismales ou des cardiopathies infectieuses[13]. Les autres causes sont les cardiopathies toxiques [éthylisme chronique, post-chimiothérapie (p.ex. anthracyclines)] et les cardiomyopathies dilatées "idiopathiques" dont l'étiologie n'est pas encore établie mais dont l'origine génétique est probablement prépondérante.

2.1.4 *Physiopathologie et remodelage ventriculaire gauche*

La finalité de la fonction cardiaque est d'assurer un débit cardiaque suffisant afin d'assurer les apports métaboliques nécessaires à l'ensemble des organes. Lorsqu'il existe une diminution de ce débit cardiaque, à des stades infra-cliniques asymptomatiques, des phénomènes compensateurs se mettent en place. Il s'agit généralement d'une hypertrophie cellulaire et ventriculaire gauche[16,17]. Ces mécanismes adaptatifs sont habituellement

regroupés sous le terme de remodelage ventriculaire gauche. Celui-ci se réalise à différents niveaux : myocarde, myocytes et protéines myocytaires. Une définition unique du remodelage est complexe voire impossible. Celui-ci débute probablement par une reprogrammation du génotype des cellules du myocarde (augmentation de la synthèse protéique et modification du phénotype protéique pro-hypertrophique).

Ces adaptations initialement bénéfiques (augmentation du nombre d'éléments contractiles mais également de leur volume conduisant à une augmentation de l'épaisseur des parois ventriculaires, entraînant une diminution de la tension pariétale et une augmentation du volume d'éjection systolique[16]) ont un effet à long terme délétère conduisant à un remodelage pathologique par dilatation et diminution de la fonction systolique du ventricule gauche. Il apparaît donc progressivement une hypertrophie ventriculaire gauche ainsi qu'une déstructuration de la microarchitecture. La géométrie ventriculaire gauche change : le ventricule gauche perd son aspect elliptique et se sphérise[18], conduisant à une diminution de la fonction systolique. Les myocytes s'hypertrophient et s'allongent mais deviennent moins nombreux. Si aucune prise en charge n'est débutée, un cercle « vicieux » s'installe pouvant être accéléré par des épisodes aigus intercurrents[19] (p.ex. infarctus du myocarde) mais surtout par une activation chronique des systèmes rénine-angiotensine-aldostérone et catécholaminergique[20]. (Figure 2)

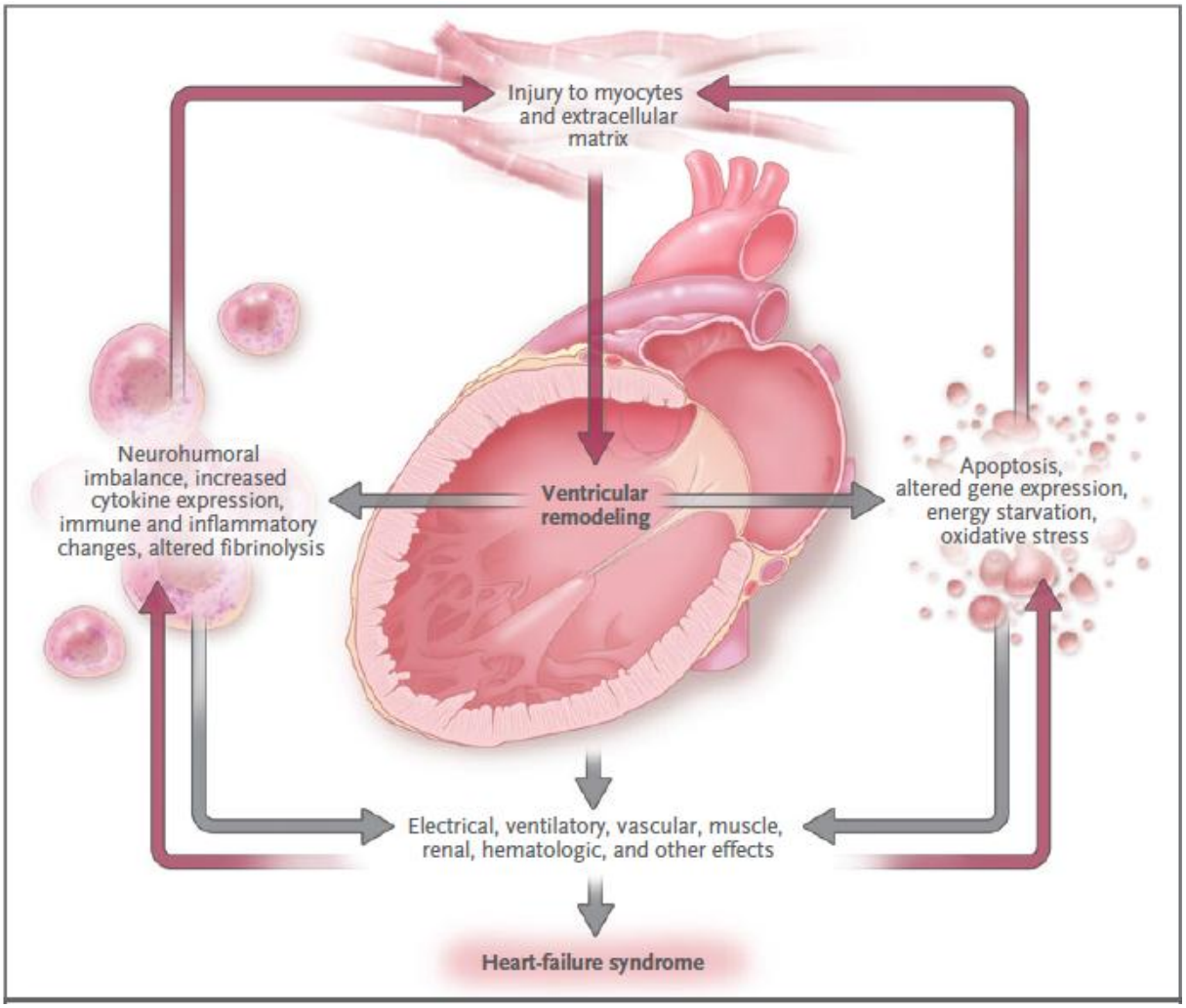


FIGURE 2: McMurray JJV. N Engl J Med 2010;362: 228–238.

Les concentrations élevées de norépinephrine plasmatique des patients insuffisants cardiaques[21], traduisant une activation du système sympathique, sont liées à un pronostic péjoratif[22]. De plus, des concentrations élevées d'aldostérone sanguine chez des patients présentant une insuffisance cardiaque chronique sont des facteurs prédictifs indépendants de sur-mortalité[23].

L'activation de ces deux systèmes favorise le remodelage délétère du ventricule gauche. Celui-ci augmente le risque de survenue de décès par IC terminale ou par mort subite qui sont les deux principales causes de décès de l'IC. Ce remodelage délétère se traduit notamment par une augmentation des concentrations de calcium intra-myocytaire, des dépôts de fibrose favorisant les troubles du rythme ventriculaires graves mais aussi une

vasoconstriction, une apoptose[24,25] et une rétention hydro-sodée.

Nous aborderons plus tard le rôle majeur de la fibrose myocardique. Chez les patients insuffisants cardiaques, la diminution du Ca^{2+} dans le réticulum sarcoplasmique et par conséquent l'augmentation des concentrations de Ca^{2+} intra-cytoplasmique diastolique est due à différents mécanismes[26] (Figure 3) :

- Diminution de l'expression de la SERCA (pompe Ca^{2+}-ATPase du réticulum sarcoplasmique qui pompe le Ca^{2+} intracellulaire vers le réticulum sarcoplasmique)[26]

- Augmentation de l'inhibition de la SERCA par le phospholamban déphosphorylé[27,28]

- Sortie du Ca^{2+} du réticulum sarcoplasmique créant des « sparks » en phase 4 du potentiel d'action favorisée, en diastole, par les canaux à la ryanodine fuyants. Ces étincelles favorisent la survenue de post-dépolarisations tardives et donc de troubles du rythme ventriculaires graves[29,30]

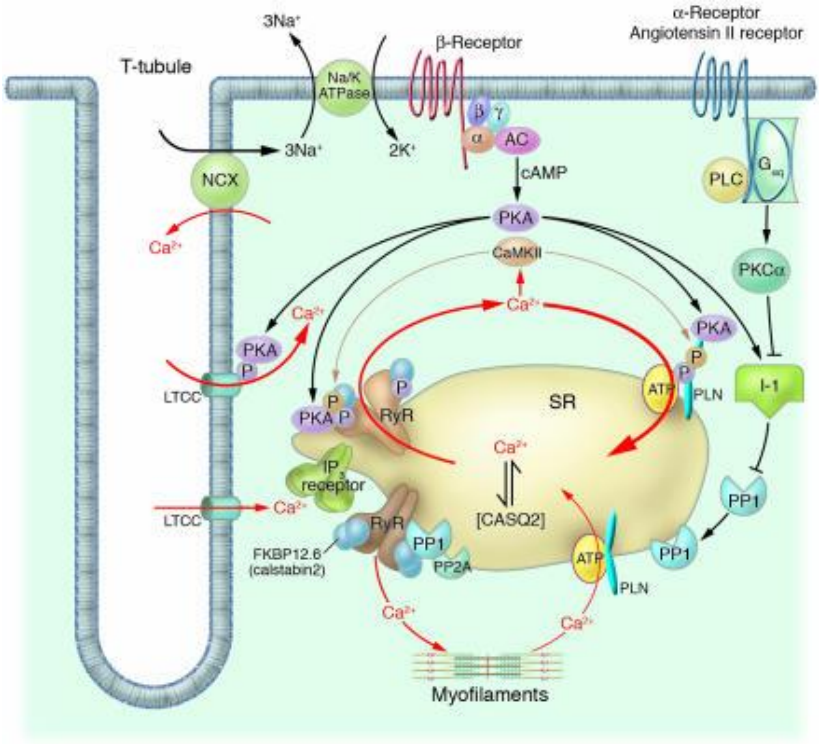


FIGURE 3: Rubart M, Zipes DP. Mechanisms of sudden cardiac death. J. Clin. Invest. 2005; 115:2305–2315.

2.1.5 *Thérapeutiques*

Basés sur les concepts physiopathologiques décrits plus haut, les traitements modernes de l'IC à fonction systolique altérée ont pour but d'inhiber l'activation excessive délétère des systèmes rénine-angiotensine-aldostérone et catécholaminergique[5,31,32].

Ces innovations thérapeutiques ont permis une amélioration franche du pronostic des patients insuffisants cardiaques à fonction systolique altérée[33,34]. De nombreuses études ont permis de valider l'utilité des inhibiteurs de l'enzyme de conversion[35–37], des bêta-bloquants[38–41] et des antagonistes des récepteurs aux minéralocorticoïdes[42–44] chez les patients IC à fonction systolique du ventricule gauche altérée. Les recommandations de la société européenne de Cardiologie ont clairement mis au centre de la prise en charge ces trois classes[5].

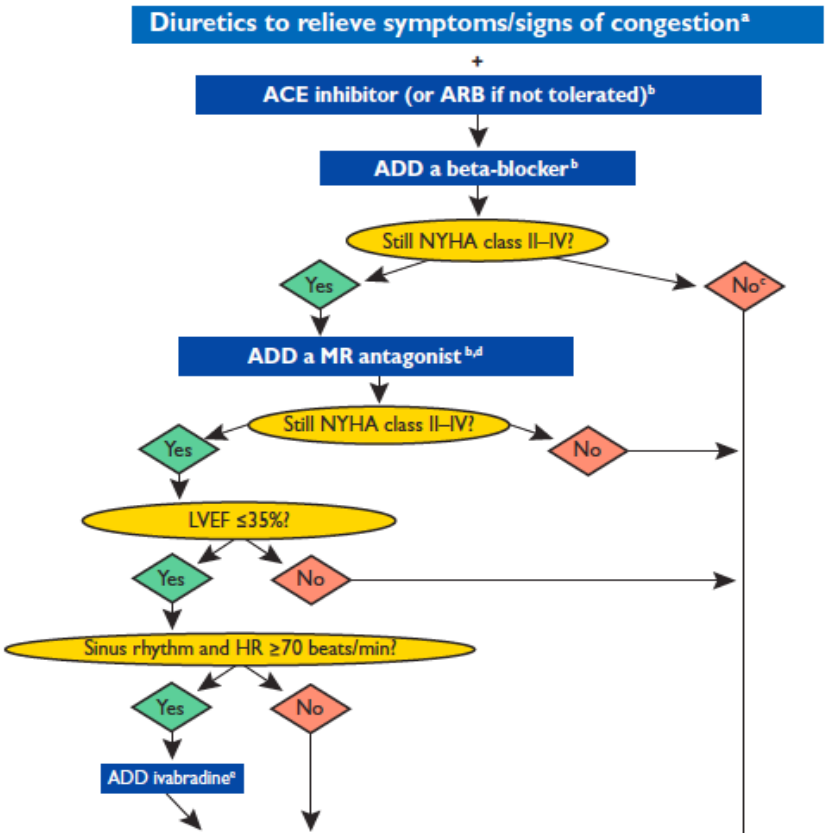


FIGURE 4: McMurray JJV, ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. *Eur. J. Heart Fail.* 2012; 14:803–869.

2.2 Obésité Abdominale

2.2.1 *Définition*

L'obésité est définie par un Indice de Masse Corporelle[45] (IMC) supérieur à 30 kg/m^2. Le surpoids correspond à un IMC compris entre 25 et 29.9 kg/m^2.

L'obésité abdominale, évaluée par la mesure du tour de taille, est un facteur de risque cardiovasculaire à part entière[46–48]. Elle est appelée « abdominal obesity » ou « normal weight obesity » en Anglais confirmant la physiopathologie particulière de ce trouble indépendant de l'obésité « traditionnelle » évaluée par l'IMC.

Selon les recommandations de la Fédération Internationale de Diabétologie, l'obésité abdominale est définie par un tour de taille > 88 cm chez la femme et > 102 cm chez l'homme pour la population « nord-américaine » alors que pour la population « européenne » les limites sont respectivement de 80 et 94 cm[49]. Le tour de taille permet une évaluation de la graisse abdominale péri-viscérale, maintenant identifiée comme un facteur de risque cardiovasculaire indépendant. Le ratio tour de taille / tour de hanche est plus informatif du degré d'obésité abdominale que l'IMC[50,51]. Ce rapport permet de différencier une obésité abdominale de type androïde (rapport > 1), à fort risque cardiovasculaire, d'une obésité de type gynoïde (rapport < 1).

L'obésité abdominale est l'élément central du syndrome métabolique. Ce dernier est un score composite reprenant l'ensemble des anomalies métaboliques (hyperglycémie à jeun, hypertriglycéridémie, hypoHDLémie, hypertension artérielle) associées chez les patients présentant une obésité abdominale.

2.2.2 *Epidémiologie*

L'incidence et la prévalence du syndrome métabolique sont en pleine croissance principalement dans les pays développés. La prévalence varie de 9,8% à 25% selon le sexe et les populations[52–55].

La prévalence de l'obésité est en croissance exponentielle dans l'ensemble des populations[56–64] tout comme celle de l'obésité abdominale[58–60,63,65].

2.2.3 *Rôle du tissu adipeux central*

De nombreux modèles animaux ont été créés pour étudier l'impact de l'obésité sur le système cardiovasculaire mais surtout les mécanismes en cause : souris déficientes en leptine normale (*ob/ob* mice)[66] ou mutées sur le gêne du récepteur de la leptine[67], modèle KKAy (altération de la voie de signalisation de la mélanocortine)[68], ou plus spécifiquement des modèles développant une obésité abdominale et une hypertension artérielle par expression de 11βHSD dans le tissu adipeux[69].

Des modèles transgéniques ont également été créés afin de développer un modèle de cardiopathie lipotoxique majoritairement en augmentant la consommation d'acides gras saturés dépassant ainsi les capacités d'oxydation mitochondriales (surexpression de PPARα[70], rat Zucher *fa/fa* avec mutation du gène du récepteur de la leptine[71]).

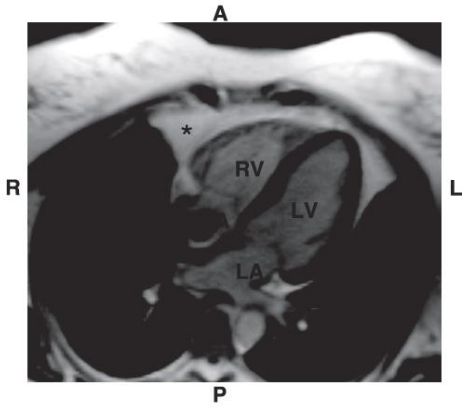


FIGURE 5: Abel ED, Cardiac remodeling in obesity. Physiol Rev. 2008 Apr;88(2):389-419.

Le tissu adipeux central, péri-viscéral, est l'élément clé expliquant le rôle péjoratif de l'obésité abdominale. Il a une activité endocrine intense. Certes l'obésité peut par différents mécanismes conduire à des modifications structurelles et fonctionnelles (augmentation de l'utilisation des acides gras[72] et diminution du glucose[73], dysfonction mitochondriale[74], insulino-résistance[75], inflammation[76,77], surcharge de pression et de volume[16], apoptose[78]) mais l'impact du tissu adipeux péri-viscéral est majeur et implique différentes voies évoquées ci-dessous.

2.2.3.1 ***Activation neurohormonale locale***

Elle correspond à l'implication du système rénine-angiotensine au niveau du tissu adipeux péri-viscéral[79,80] avec augmentation locale de la sécrétion de l'angiotensinogène[81]. Cette activation va conduire à une mise en jeu accrue des systèmes rénine-angiotensine et catécholaminergique systémiques participant ainsi au remodelage cardiovasculaire[82].

2.2.3.2 ***Rôle des adipokines[83]***

Les adipokines ou « hormones sécrétées par le tissu adipeux » ou adipocytokines sont des cytokines secrétées par le tissu adipeux. L'effet autocrine et paracrine des adipokines aboutit à une action directe sur le myocarde ou sur la graisse péricardique[84,85]. Les deux adipokines les plus étudiées sont la leptine et l'adiponectine. Nous évaluerons leur impact sur le remodelage cardiovasculaire.

2.2.3.2.1 L'adiponectine

L'adiponectine est l'une des protéines plasmatiques les plus abondantes[86,87]. Il existe 3 formes actives oligomériques, la partie C-terminale isolée a également une activité biologique[88,89]. Les concentrations d'adiponectine diminuent habituellement chez les

patients diabétiques et obèses[90]. L'adiponectine se lie à deux récepteurs[87] dont l'AdipoR1 est le plus fréquent dans le système cardiovasculaire[91,92].
Ses rôles physiologiques communément admis sont ses actions anti-diabétique, anti-inflammatoire, anti-athérosclérotique et cardioprotectrice[87,93–95]. La majoration de l'apoptose et du dépôt de fibrose chez des souris « adiponectin – knockout » (Ad-KO) illustre ce rôle protecteur[87].

L'adiponectine intervient positivement sur le remodelage cardiovasculaire par différentes voies et via différents effets:

2.2.3.2.1.1 Métabolique

- Augmentation de l'absorption des acides gras mais également de leur oxydation réduisant *in fine* l'accumulation lipidique par activation de la voie des MAPkinases[96].
- Augmentation de la sensibilité à l'insuline et de l'oxydation glucidique[92].

2.2.3.2.1.2 Anti-apoptotique

L'adiponectine a également un effet cardio-protecteur par son action anti-apoptotique par différentes voies de signalisation (MAPKinases[97], AdipoR1-APPL1[98]) en augmentant notamment les capacités anti-oxydantes des cellules après une hypoxie notamment. Cela conduit à une diminution de la taille de la surface infarcie au décours d'un infarctus du myocarde[96,99,100].

2.2.3.2.1.3 Anti-fibrotique

Les études sur les souris Ad-KO ont permis d'appréhender l'impact de l'adiponectine sur la fibrose myocardique. En effet, ces souris développent une fibrose majeure qui diminue par

l'ajout d'adiponectine[96,99,101,102] et augmente (majoration du collagène de type I et III) par l'apport d'angiotensine II[103]. L'action de l'adiponectine se ferait par altération de l'activité et de l'expression des différentes isoformes des métalloprotéinases.

2.2.3.2.1.4 Anti-hypertrophique

Plusieurs études animales et humaines[104] ont mis en évidence l'effet anti-hypertrophique de l'adiponectine notamment par la voie des MAP Kinases en inhibant l'effet hypertrophique de l'angiotensine II[105], mais aussi par un effet direct sur le cardiomyocyte via l'action PPAR-γ[106]. Cet effet anti-hypertrophique de l'adiponectine a été confirmé par le développement d'hypertrophie intense chez les souris Ad-KO[96,99,105,107].

2.2.3.2.2 La leptine

La leptine est produite par le tissu adipeux mais également par d'autres organes, notamment le cœur (rôle de la graisse épicardique, Figure 4), la graisse péri-vasculaire et l'estomac[108]. La leptine est décrite comme intervenant dans la régulation de l'appétit favorisant la prise de poids puisque corrélée au niveau de satiété[109]. Les concentrations sont habituellement élevées chez les sujets obèses du fait d'une leptino-résistance[110,111] secondaire à un déficit de régulation des apports nutritionnels par l'hypothalamus[110,111]. Une corrélation positive existe entre les concentrations élevées de leptine et les évènements cardiovasculaires (Figure 6) comme l'hypertension artérielle, l'athérosclérose, l'infarctus du myocarde[112].
Les effets de la leptine peuvent être directs sur le cœur ou via une atteinte vasculaire (Figure 7):

2.2.3.2.2.1 Métabolique

La leptine augmente l'oxydation des acides gras et donc la consommation en oxygène du

myocarde par la voie des MAPKinases[113]. A la différence de l'adiponectine, la leptine n'a a priori pas d'effet sur le métabolisme glucidique[114,115].

2.2.3.2.2.2 Anti-apoptotique

La leptine a, *in vivo*[116] et dans différents modèles animaux, un effet anti-apoptotique et donc cardio-protecteur[117,118].

2.2.3.2.2.3 Pro-hypertrophique

Il est admis que la leptine a un effet hypertrophique sur les cardiomyocytes aussi bien chez l'homme que dans les modèles animaux[119,120] via la voie de signalisation p38 MAP kinase[121].
Il existe aussi probablement une relation en U entre la concentration en leptine et le degré d'hypertrophie cardiomyocytaire. En effet les souris *ob/ob* (déficitaires en leptine normale) développent une hypertrophie[116] régressant après infusion de leptine[122].

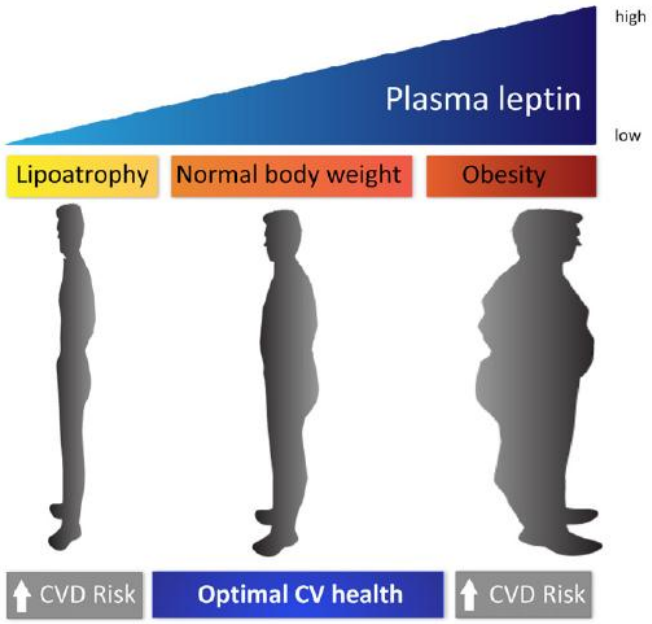


FIGURE 6: Abel ED, Modulation of the cardiovascular system by leptin. Biochimie. 2012 Oct;94(10):2097-103.

2.2.3.2.2.4 Pro-fibrotique

Même si les travaux ne sont pas encore très développés dans ce domaine, de plus en plus d'études convergent pour affirmer l'effet pro-fibrotique de la leptine. En effet les souris *ob/ob* ou les rats (*fa/fa*) Zucker développent de la fibrose myocardique[123–125].
La leptine augmente la production d'ARNm de pro-collagène de type III et IV et diminue celle de pro-collagène de type I[126] dans les cellules humaines initiales de ventricules pédiatriques. Enfin la leptine participe à l'augmentation des pro-collagènes de type I et III dans les modèles murins de cardiopathies ischémiques aiguës[127].

2.2.3.2.2.5 Pro-inflammatoire

L'inflammation est corrélée à la survenue d'évènements cardiovasculaires par une intervention sur la structure et la fonction myocardiques mais aussi au niveau vasculaire[128–130]. La leptine est probablement l'un des médiateurs les plus importants de l'inflammation. L'activation du système immunitaire inné favorise la production de leptine qui va secondairement activer les cellules inflammatoires impliquées dans l'athérosclérose comme les monocytes, les macrophages et les lymphocytes-T[110].

2.2.3.2.2.6 Hypertensif

Les patients obèses ont un risque plus important de développer une hypertension artérielle. Les concentrations de leptine sont positivement associées à la pression artérielle y compris aux stades précoces chez des patients normotendus[131].
La leptine exerce un effet vasopresseur et diminue la natriurèse par activation du système sympathique[132].

2.2.3.2.2.7 Athérosclérotique

La leptine favorise et accélère la survenue d'athérosclérose par différents mécanismes, notamment par stimulation intimale de monocytes, transformation des cellules macrophagiques, prolifération des cellules musculaires lisses et sécrétion de cytokines pro-athérosclérotiques[133].

2.2.3.2.2.8 Dysfonction endothéliale

La dysfonction endothéliale est habituellement décrite comme un état précurseur à l'athérosclérose et à la dysfonction diastolique du ventricule gauche. La leptine induit une perturbation de la balance de monoxyde d'azote caractéristique de la dysfonction endothéliale[134]. Ces anomalies surviennent possiblement à des concentrations supra-physiologiques de leptine[108].

2.2.3.2.2.9 Pro-thrombotique

La leptine a un effet agrégant plaquettaire concentration dépendant[135]. De plus les plaquettes des sujets obèses ont une sensibilité particulière à la leptine expliquant le sur-risque de thrombose aiguë et donc de syndrome coronarien aigu chez les patients obèses[136]. Cet état est confirmé par la diminution du risque de thrombose chez les souris *ob/ob*[137]. La voie de la phosphodiestérase est possiblement impliquée dans cette action pro-agrégante[138].

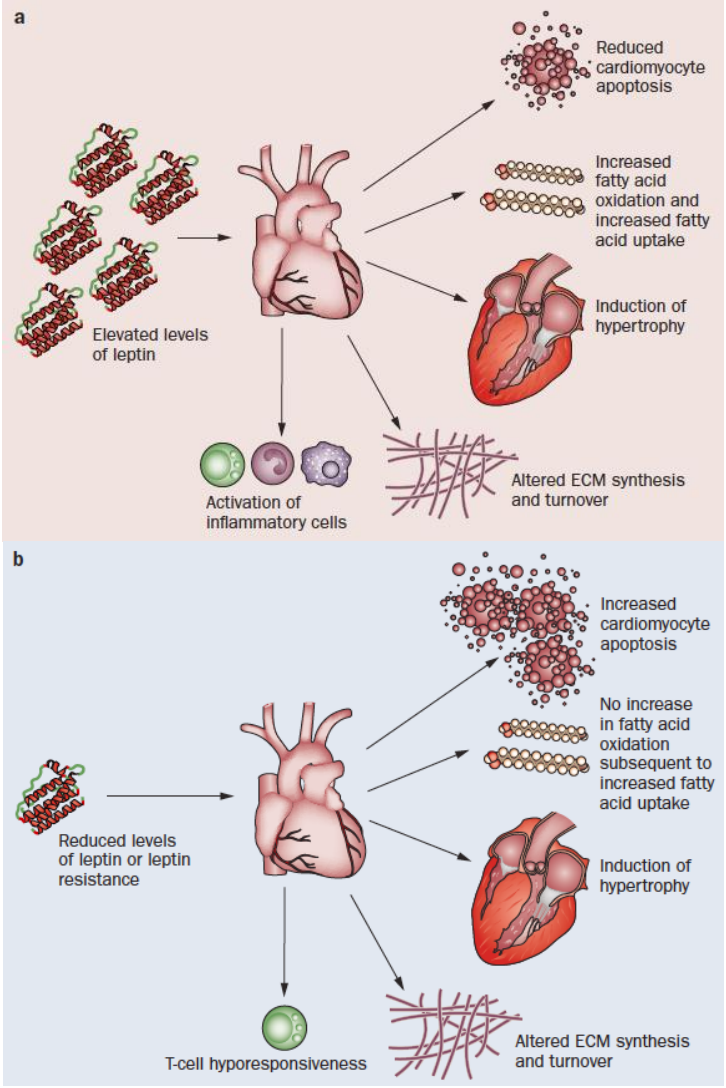


FIGURE 7: Sweeney G, Cardiovascular effects of leptin. Nat Rev Cardiol. 2010 Jan;7(1):22-9.
A: Effets de la leptine à des concentrations élevées. B: Effets de la leptine à des concentrations faibles ou en cas de résistance.

2.2.4 *Complications de l'obésité abdominale*

L'obésité seule est à l'origine de 11 % des cas d'IC chronique chez l'homme et 14% des cas chez la femme aux Etats-Unis. La cohorte Framingham a permis l'analyse de la relation entre l'IMC et le risque de survenue d'IC chronique chez plus de 5880 participants. Après 14 années de suivi, 496 personnes ont développé une IC chronique. Le risque d'être atteint de cette affection s'accroît de 5% chez les hommes et de 7% chez les femmes pour chaque augmentation d'1 point de l'IMC. Ainsi, par rapport aux sujets ayant un IMC normal

(compris entre 19 et 24,9 kg/m^2), le risque de survenue d'IC double chez les sujets obèses[139].

Il est actuellement établi qu'il existe un « paradoxe de l'obésité ». En effet dans la population générale le surpoids et l'obésité sont associés à une surmortalité[66,140] alors que les patients IC ou porteurs de cardiopathies ischémiques avec un IMC élevé ont une mortalité plus faible[141,142]. Par ailleurs, plusieurs études[143,144] tendent à contredire l'existence de la cardiomyopathie de l'obèse, communément admise jusqu'à présent.

De plus le risque est également plus élevé à IMC constant chez les patients obèses en fonction du rapport tour de taille / tour de hanche[145]. L'obésité abdominale est indépendamment associée à une surmortalité dans la population générale[146,147] et chez les patients porteurs de cardiopathie ischémique[148]. Il est également préférable d'associer l'IMC à l'obésité abdominale pour discriminer le risque cardiovasculaire de façon plus précise. Les patients ischémiques avec un IMC normal mais porteur d'une obésité abdominale ont une moindre survie en comparaison aux patients obèses sans atteinte abdominale mais surtout aux patients atteints des deux pathologies (IMC élevé et obésité abdominale)[149].

Des changements structurels et fonctionnels sont habituellement décrits chez des patients obèses, expliquant l'évolution vers l'IC indépendamment de la survenue d'un infarctus, d'hypertension artérielle ou de diabète :

- hypertrophie ventriculaire gauche évaluée par la masse ventriculaire gauche indexée à la surface corporelle, ou à la masse maigre (permettant de diminuer le risque de surestimation sexe–dépendant[150,151]). Cette augmentation de la masse ventriculaire est due à une augmentation de l'épaisseur des parois musculaires mais également à une augmentation du dépôt graisse épicardique et intra myocardique[152]. Cette augmentation est par ailleurs souvent associée à une dilatation du ventricule gauche.
- Augmentation des volumes et de l'épaisseur du ventricule droit[153,154]. Malheureusement il est difficile de faire la part des choses entre l'impact de l'obésité et celui des pathologies respiratoires associées, notamment le syndrome d'apnée du

sommeil.

- Augmentation de la taille de l'oreillette gauche, possiblement secondaire à l'augmentation du volume circulant, de l'hypertrophie ventriculaire gauche et des pressions de remplissage. Cette augmentation est associée à un sur-risque de survenue de fibrillation atriale[155].
- Dépôt de fibrose interstitielle myocardique : ceci a été mis en évidence chez les rongeurs avec possiblement un dépôt initialement péri-vasculaire suivant les modèles utilisés[125,156,157]. Ce dépôt de fibrose est corrélé à l'activation des voies du plasminogen activator inhibitor 1 (PAI-1), du transforming growth factor (TGF), et de la Jun NH2-terminal kinase (JNK). Celui-ci est diminué par l'utilisation des antagonistes du système rénine-angiotensine-aldostérone[158,159].
- Atteinte de la fonction systolique du ventricule gauche : comme déjà expliqué précédemment la cardiomyopathie de l'obèse traditionnellement décrite est actuellement remise en question. Il existe vraisemblablement une courbe en U associant l'IMC à la morbi-mortalité cardiovasculaire avec un sur-risque chez les patients à IMC bas ou très élevé et un effet protecteur chez les patients avec un poids normal, en surpoids ou en légère obésité[160,161].

2.3 INFARCTUS DU MYOCARDE

2.3.1 *Définition*

L'athérosclérose coronaire est une affection inflammatoire chronique émaillée de poussées aiguës. Celles-ci déclenchent une ischémie caractérisant les syndromes coronariens aigus qui peuvent être dus à une thrombose complète d'une artère coronaire (syndrome coronarien aigu avec sus décalage du segment ST) ou à un déséquilibre transitoire entre les besoins et les apports en oxygène pour la consommation des cellules myocardiques secondaire à une sténose significative coronaire (syndrome coronarien sans sus décalage du segment ST).

Les syndromes coronariens aigus avec sus décalage du segment ST sont, dans la majorité des cas, liés à une rupture de plaque athéroscléreuse. La rupture de la chape fibreuse qui sépare la masse athéroscléreuse du volume circulant met en contact le cœur lipidique avec différents facteurs de l'agrégation plaquettaire. Ceci conduit à une thrombose de la lumière vasculaire. Il peut également se produire une simple érosion de la plaque entraînant les mêmes complications. La thrombose peut être très extensive (traitée par thrombo-aspiration à la phase aiguë) ou se fragmenter et entrainer une pluie d'emboles distaux allant occlure la microcirculation[162].
Ce déséquilibre entre les besoins et les apports en oxygène des cellules myocardiques se traduit initialement par une ischémie qui en l'absence de « réouverture » de l'artère évoluera vers la nécrose myocardique traduisant la mort cellulaire[162].

2.3.2 *Épidémiologie*

La cardiopathie ischémique est la cause la plus fréquente de décès à travers le monde. Plus de 7 millions de patients décèdent par an d'une cardiopathie ischémique soit environ 12,8% de l'ensemble des causes de décès[163]. La fréquence est plus élevée chez les hommes que chez les femmes même si l'écart se réduit rapidement[164] avec un âge moyen de 63,3 ± 15,5 ans.

De plus, grâce aux nombreux efforts et progrès dans les domaines de la prévention primaire l'incidence des syndromes coronariens aigus avec sus décalage du segment ST diminue au contraire de celle de ceux sans sus décalage[165].

2.3.3 *Complications*

Les complications du syndrome coronarien aigu avec sus décalage du segment ST sont multiples. Les plus connues et classiques sont les complications aiguës ou sub-aiguës, comme : le décès, le choc cardiogénique, l'évolution anévrysmale du territoire infarci du ventricule gauche, les troubles de conduction auriculo-ventriculaire, les troubles du rythme ventriculaires ou supra-ventriculaires, le thrombus intra-VG, la présence d'un régurgitation mitrale ischémique, le syndrome pleuro-péricardique de Dressler, les ruptures cardiaque internes (communication inter-ventriculaire) ou externes, une extension ventriculaire droite du syndrome coronarien aigu inférieur[166].

La mortalité intra-hospitalière des patients pris en charge pour syndrome coronarien avec sus décalage du segment ST varie selon les registres de 6 à 14%[167] et a même chuté à 4,4% récemment[164]. Elle reste tout de même à 12% à 6 mois[168].

La mortalité des syndromes coronariens avec sus décalage du segment ST est influencée par des éléments cliniques initiaux (âge, classe Killip, délai de prise en charge, localisation de l'infarctus, insuffisance rénale, …). Malheureusement ces derniers restent imparfaits

pour prédire le remodelage ventriculaire gauche qui est l'élément clé du devenir de ces patients à moyen et long terme.

De plus, le fait que la mortalité intra-hospitalière post infarctus chute grâce aux progrès thérapeutiques comme l'angioplastie primaire précoce modifie le devenir de ces patients. Les cliniciens ne peuvent et ne doivent plus se contenter de gérer la phase aiguë. Il est nécessaire d'anticiper et de prédire les patients qui vont développer un remodelage délétère dans le post-infarctus. Ce remodelage représente le devenir à moyen et long terme de ces patients.

Ce remodelage débute dès les premières heures après la survenue de l'infarctus comme cela a été mis en évidence dans des modèles post-infarctus[169,170].

Différentes modifications, caractérisant le remodelage, ont été observées[171–173] :

- Allongement des cardiomyocytes et diminution de l'épaisseur de la paroi ventriculaire
- Elargissement de la zone infarcie associée à une inflammation du tissu nécrotique puis à une cicatrisation
- Poursuite de l'élargissement de la zone infarcie
- Hypertrophie myocytaire initialement compensatrice
- Dilatation et remodelage du ventricule gauche
- Perte de la continuité myocytaire
- Accumulation excessive de collagène dans la matrice extracellulaire.

Les différentes voies cellulaires, responsables de ces modifications, n'ont pas encore été clairement établies, mais il existe ici également une activation locale des systèmes neuro-hormonaux favorisant l'hypertrophie myocytaire et le dépôt de fibrose. Ces modifications ont initialement un effet réparateur en réponse à la nécrose myocardique qui sera sur le moyen et le long terme délétère. Plus la nécrose myocardique initiale est importante plus le remodelage ventriculaire gauche est intense avec une dilatation plus importante[173].

2.4 PEPTIDES COLLAGÉNIQUES SANGUINS

2.4.1 *Matrice extracellulaire*

Les myocytes et les fibroblastes sont maintenus par la matrice extracellulaire. Celle-ci correspond à un réseau de fibres protéiques principalement collagéniques. Dans un cœur adulte sain, le collagène représente 2 à 4% du myocarde[174]. Il existe un équilibre entre la production et la dégradation de ces fibres en réponse à l'ischémie, la tension pariétale, et l'inflammation par exemple[175]. Le réseau collagénique est métaboliquement actif. La durée de son turnover est évaluée entre 80 et 120 jours[176].

Les deux types de fibres collagéniques les plus fréquentes sont habituellement les fibres de type I et III. Les fibres de type I sont les plus représentées dans le cœur sain (85%), mais sont peu spécifiques de cet organe. Elles ont un rôle de résistance et confèrent au myocarde sa rigidité. Les fibres de type III sont moins présentes (10%) mais sont plus spécifiques du cœur. Elles possèdent des propriétés élastiques [174,175,177,178].

2.4.2 *Peptides collagéniques*

Les fibres de collagène sont initialement synthétisées sous forme de molécules de procollagène de type I et III qui seront ensuite dégradées par des métalloprotéinases spécifiques (MMPs) en pro-peptides C-terminaux (PICP, PIIICP) et pro-peptides N-terminaux (PINP : aminoterminal propeptide of type I procollagen, PIIINP : aminoterminal propeptide of type III procollagen) en proportions équivalentes. L'activité des MMPs est inhibée par les « tissue inhibitors of metalloproteinases » (TIMPs). Il existe donc un équilibre entre les MMPs et les TIMPs permettant ainsi de conserver l'architecture de la MEC. (Figure 8).

Les pro-peptides N et C-terminaux sont considérés comme des marqueurs de la synthèse collagénique au contraire de l'ICTP (collagen type I cross-linked carboxy-terminal propeptide) qui est un marqueur de la dégradation du collagène de type I. Les peptides collagéniques PINP, PICP et PIIINP, marqueurs de la synthèse de fibrose et l'ICTP sont obtenus par dégradation 1:1 des pro-peptides. Il est important de noter que le PIIINP, à la différence du PICP pour le type I, n'est pas toujours obtenu lors du clivage du pro-collagène de type III. Ceci peut conduire à une sous-estimation des concentrations en PIIINP[179].

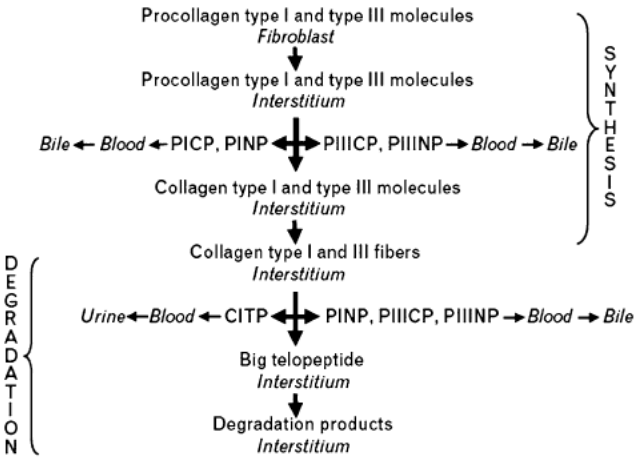


FIGURE 8: Zannad F, Extracellular matrix fibrotic markers in heart failure. Heart Fail Rev. 2010 Jul;15(4):319-29.

Les peptides collagéniques ne sont pas spécifiques du myocarde. Ils peuvent en effet être également produit par les os, le foie, les reins ou les poumons[180]. Mais la corrélation entre les concentrations sériques des peptides collagéniques et les données anatomopathologiques myocardiques est établie[180–182]. Enfin ceux-ci peuvent également être sécrétés directement par le cœur[183]. L'élimination des ces peptides collagéniques se fait selon différentes voies : hépatiques (PIIINP, PICP) ou urinaires (ICTP)[184].

Grâce à différentes études le PIIINP a été identifiés comme un facteur prédictif d'évènements dans l'IC à fonction systolique préservée[185], dans l'IC chronique[186,187], dans le post-infarctus[188] ou dans les cardiomyopathies dilatées[180,189] pour le PIIINP. Il en est de même pour l'ICTP en post-infarctus du myocarde[190], dans l'IC à fonction systolique préservée[191] ou chez les patients symptomatiques porteurs d'une cardiopathie hypertensive[192] (Table 1).

Peptides collagéniques	***Pathologies***	***Évènements associés***	***Références***
PIIINP	Insuffisance cardiaque à fonction systolique préservée	Décès toute cause et hospitalisations cardiovasculaires	179
PIIINP	IC chronique à fonction systolique altérée	Décès et hospitalisation pour IC	180
PIIINP	IC chronique à fonction systolique altérée (RALES sub-study)	Décès ou Décès + hospitalisation pour IC	181
PIIINP	Post-IDM	Décès et développement d'IC	182
PIIINP	Cardiomyopathies dilatées	Morbi-mortalité (décès, transplantation, IC terminale)	175
PIIINP	Cardiomyopathies dilatées	Décès cardiovasculaires ou hospitalisation pour IC	183
ICTP	Post-IDM	Décès toute cause et développement d'IC	184
ICTP	IC à fonction systolique préservée	Décès cardiovasculaire et aggravation d'IC	185
ICTP	Cardiopathies hypertensives	Diminution du strain radial et global du ventricule gauche	186

TABLE 1 : récapitulatif des associations publiées dans la littérature entre les pathologies cardiovasculaires et les peptides collagéniques.

Les MMPs et les TIMPs, traduisent l'activité du turnover de la matrice à la différence des peptides collagéniques. Mais il n'y a jamais eu de corrélation établie entre les concentrations sériques des MMP-1 et TIMP-1 et des données anatomopathologiques à la

différence des peptides collagéniques[193]. C'est pour cette raison que nous avons fait le choix d'étudier le rôle des peptides collagéniques.

Enfin, il existe tout de même certaines limites à l'utilisation de ces marqueurs comme le fait qu'ils ne soient pas spécifiques du myocarde[180]. De plus de nombreuses voies d'élimination (hépato-biliaire, urinaire) peuvent interférer avec les concentrations sanguines des peptides collagéniques dans des populations présentant de nombreuses comorbidités comme les patients insuffisants cardiaques[194].

Le PINP n'a pas été retrouvé associé aux pronostics dans différentes cardiopathies. Il existe un retard de clivage du PINP par rapport au PICP dans les kits de dosages utilisés. Ceci pourrait expliquer l'association du PICP mais pas du PINP aux pronostics dans différentes cardiopathies[179].

2.4.3 *Fibrose myocardique*

Les modifications de l'équilibre de la matrice extracellulaire peuvent conduire à la production de fibrose cardiaque (dépôt de collagène). Cette fibrose est l'un des éléments majeurs de la survenue du remodelage ventriculaire gauche dans différentes cardiopathies (cardiomyopathies dilatées, cardiopathies hypertrophiques post hypertensives, cardiopathies ischémiques).

Deux types d'accumulation de fibrose myocardique[174] sont décrits :

- Le type réactif :

Il fait suite à une réaction initiale fibrotique péri-vasculaire avec extension interstitielle après une atteinte vasculaire coronaire[177,195].

- Le type réparateur :

Il permet la constitution d'un tissu cicatriciel, suite à une perte de substance en cardiomyocytes après nécrose, par accumulation de collagène[172,196–198].

Enfin le dépôt de fibrose est dépendant de nombreuses voies comme le TGF-β qui le favorise[199,200], comme les cytokines inflammatoires[201,202], et l'activation du système rénine angiotensine[203]. La fibrose est un des éléments clé du pronostic des patients insuffisants cardiaques en favorisant la rigidité ventriculaire et l'hétérogénéité myocardique conduisant au risque de mort subite et d'insuffisance cardiaque terminale (Figure 9).

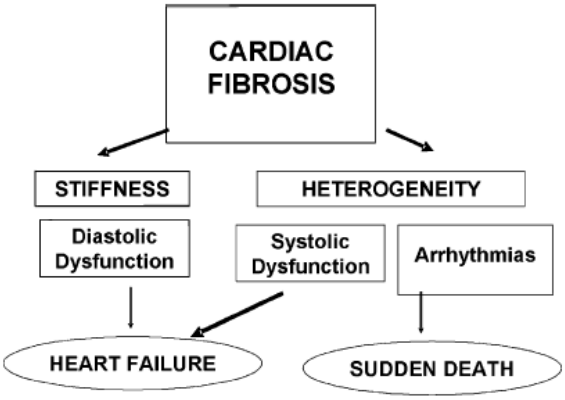


FIGURE 9: Zannad F, Extracellular matrix fibrotic markers in heart failure. Heart Fail Rev. 2010 Jul;15(4):319-29.

3 OBJECTIFS

La recherche de marqueurs sanguins prédictifs du remodelage délétère du ventricule gauche par leur impact physiopathologique et potentiellement thérapeutique connaît une croissance exponentielle depuis plusieurs années. Ce domaine intéresse de nombreux chercheurs du fait des possibilités thérapeutiques mais également car il s'agit d'un problème de santé publique majeur. Il est clairement établi que la fibrose est un excellent marqueur de l'évolution délétère éventuelle du remodelage ventriculaire gauche. L'un des moyens les plus informatifs et les moins invasifs pour évaluer la fibrose et le remodelage tissulaire du ventricule gauche est l'analyse des biomarqueurs du collagène de la matrice extracellulaire. L'impact du dépôt initial de fibrose myocardique sur le remodelage ventriculaire gauche post infarctus du myocarde a été mis en évidence[204], ainsi que l'effet anti-fibrotique de certaines classes thérapeutiques, principalement les antagonistes des récepteurs aux minéralocorticoïdes dans des populations sévères[187,204].

De nombreuses études se sont intéressées aux mécanismes de transition de l'hypertension artérielle, du diabète vers l'insuffisance cardiaque. Beaucoup moins concernaient l'obésité. Quasiment aucune étude n'a pris le parti d'étudier et de rechercher les possibles mécanismes de transition indépendant des autres facteurs de risque (hypertension artérielle, diabète, obésité, infarctus du myocarde) de l'obésité abdominale vers l'insuffisance cardiaque.

Enfin, très peu d'études ont recherché l'intérêt prédictif des peptides collagéniques sur le remodelage ventriculaire gauche et la survie, chez des patients présentant un syndrome coronarien aigu non compliqué et idéalement traités.

L'objectif de ce travail était d'évaluer l'intérêt des peptides collagéniques aux différents stades de l'évolution de l'insuffisance cardiaque, et de répondre à trois questions:

- la fibrose myocardique est-elle déjà présente et associée à des anomalies structurelles ou fonctionnelles cardiaques et artérielles chez des patients asymptomatiques présentant une obésité abdominale (stade A) ?
- les peptides collagéniques peuvent-ils apporter une information supplémentaire aux cliniciens afin de mieux identifier les patients à haut risque de remodelage ventriculaire gauche à 1 an et de morbi-mortalité à 3 ans en post infarctus du myocarde (stade B) ?
- les antagonistes des récepteurs aux minéralocorticoïdes, thérapeutique anti-fibrotique de référence, sont-ils sûrs et efficaces chez des patients moyennement symptomatiques mais avec des comorbidités majeures à haut risque de remodelage (stade C) ?

4 RÉSULTATS

4.1 MODIFICATIONS PHYSIOPATHOLOGIQUES AU STADE A: OBÉSITÉ ABDOMINALE

Comme explicité précédemment l'obésité abdominale connaît une croissance exponentielle. Elle est indépendamment (des autres facteurs de risque cardiovasculaires : hypertension artérielle, dyslipidémie, diabète) associée à un risque de survenue d'insuffisance cardiaque. Il est intéressant d'étudier les mécanismes physiopathologiques potentiels de transition vers l'IC de l'obésité abdominale.

L'objectif de ce travail était de rechercher l'existence chez des patients asymptomatiques présentant une obésité abdominale, indemnes d'obésité morbide, d'hypertension artérielle ou de diabète, de modifications structurelles et/ou fonctionnelles cardiaques et artérielles par un phénotypage extensif: clinique, électrique, biologique, échocardiographique, vasculaire et imagerie par résonnance magnétique.

Pour ce faire nous avons recruté des patients d'un âge moyen (entre 40 et 65 ans) sans autre facteur de risque cardiovasculaire répartis en deux groupes appariés par l'âge et le sexe. Notre population finale est constituée de 169 patients : 116 sujets présentant une obésité abdominale et 53 contrôles.

Nous avons pu mettre en évidence :

- la présence chez ces patients normotendus et asymptomatiques la présence d'une dysfonction diastolique, associée au PIIINP, chez près de 50% des sujets porteurs d'une obésité abdominale.
- une augmentation de la masse ventriculaire gauche et de l'index de remodelage ventriculaire gauche associés aux niveaux de pression artérielle (patients normotendus) et à la compliance artérielle.

Ces données ont fait l'objet de deux manuscrits.

4.1.1 *Features of cardiac remodeling and diastolic dysfunction are frequent in healthy subjects with abdominal obesity and are independently associated with blood pressure and fibrosis biomarkers.*

.

Romain Eschalier,M.D., Patrick Rossignol,M.D.,Ph.D., Anna Kearney-Schwartz,M.D., Chris Adamopoulos,M.D., Kyparissi Karatzidou,M.D., Renaud Fay,PharmD., Damien Mandry,M.D.,Ph.D., Pierre-Y Marie,M.D.,Ph.D., Faïez Zannad,M.D.,Ph.D.

Features of cardiac remodeling and diastolic dysfunction are frequent in healthy subjects with abdominal obesity and are independently associated with blood pressure and fibrosis biomarkers.

Eschalier *et al.*

Short Title: Cardiac remodeling in abdominal obesity patients

Romain Eschalier,M.D., Patrick Rossignol,M.D.,Ph.D., Anna Kearney-Schwartz,M.D., Chris Adamopoulos,M.D., Kyparissi Karatzidou,M.D., Renaud Fay,PharmD., Damien Mandry,M.D.,Ph.D., Pierre-Y Marie,M.D.,Ph.D., Faïez Zannad,M.D.,Ph.D.,*

From the INSERM, Centre d'Investigation Clinique CIC-P 9501, Nancy, F-54000 France (RE, PR, AKS, CA, KK, RF, FZ) ; CHU Nancy, Department of Cardiology, Nancy, F-54000 France (FZ) ; Université de Lorraine, Nancy, F-54000 France (PR, DM, PYM, FZ) ; INSERM, U1116, Nancy, F-54000 France (PR, PYM, FZ) ; Clermont Université, Université d'Auvergne, UMR6284, F-63000 Clermont-Ferrand France (RE) ; CHU Clermont-Ferrand, Department of Cardiology, F-63000 Clermont-Ferrand France (RE); CHU-Nancy, Department of Radiology, Nancy, F-54000 France (DM); CHU-Nancy, Department of Nuclear Medicine, Nancy, F-54000 France (PYM); INSERM, U947, Nancy, F-54000 France (DM).

**Corresponding Author.* Faïez Zannad, CIC Plurithématique. Institut Lorrain du cœur et des vaisseaux. 4 rue du Morvan. 54500 Vandœuvre lès Nancy – France. Tel: +33 3 83 15 73 22; Fax: +33 3 83 15 73 24; e-mail: f.zannad@chu-nancy.fr

Total Word count: 5521

Journal Subject Codes: 11, 113, 115, 148

ABSTRACT

Background. Incidence and prevalence of abdominal obesity (AO) are growing exponentially. Subjects with AO are at higher risk of developing heart failure (HF). The purpose of the study was to investigate early changes in cardiac and arterial structure and function and extracellular matrix biomarkers in 'normotensive' healthy subjects with AO.

Methods and Results. Subjects with AO and age and sex matched controls underwent echocardiography, magnetic resonance imaging [cardiac remodeling index (CRI)], carotid intima-media thickness (CIMT), pulse wave velocity (PWV) and blood fibrosis biomarkers measurements.

We enrolled 116 AO subjects and 53 controls. Although 'normotensive', AO subjects had higher systolic blood pressure (SBP) (128±16 *vs.* 116±11mmHg, p<0.0001), diastolic BP (DBP) (77±11 *vs.* 71±6mmHg, p=0.0002), left ventricle mass (97±25 *vs.* 84±21g, p=0.004), and CRI (0.69±0.16 *vs.* 0.60±0.10g/ml, p=0.004), but unchanged CIMT and PWV. Diastolic dysfunction (E'<10cm/s) could be detected in 46% of AO subjects (4% in controls). Left ventricular remodeling as assessed by LV mass or CRI was positively and independently associated with higher BP (SBP, DBP, or MBP) and AO. Higher BP, AO and procollagen-III-N-terminal peptide (PIIINP ≥2.6ng/ml) concentrations (OR 2.44 [1.05-5.69], p=0.038) were positively associated with diastolic dysfunction.

Conclusion. Early cardiac structural remodeling, fibrosis and diastolic dysfunction are detectable in healthy AO subjects. Higher BP, PIIINP, and AO were independently associated with early cardiac structural and/or functional changes. It is to be investigated whether in AO subjects an early BP reduction, even if 'normotensive', combined with weight loss, may avoid adverse cardiac remodeling and protect against progression to HF.

Key words: blood pressure; ventricular remodeling; abdominal obesity; diastolic heart failure; PIIINP.

INTRODUCTION

Obesity has reached worldwide epidemic proportions. The risk of developing chronic heart failure (HF) is higher in obese patients and more specifically so, in subjects with abdominal obesity (AO) [1,2] independently of other cardiovascular risk factors such as hypertension and diabetes mellitus. In an effort to help healthcare providers with the early identification of patients who are at risk for developing HF, the ACC/AHA 2005 classification [3] of chronic HF has insisted on the early asymptomatic stages. However, the mechanisms underlying the transition from risk factors (Stage A: patients at risk for HF but without structural heart disease or symptoms of HF) to early asymptomatic cardiac and vascular structural (stage B: patients with structural heart disease but without signs or symptoms of HF) and functional changes are still poorly understood [4]. At least in hypertension, early cardiac and vascular remodeling is the result of pressure overload and interstitial fibrosis [5]. Our group has also reported that early changes in extracellular matrix biomarkers could be detected in patients with diabetes mellitus and hypertension [6] but also in obese and otherwise healthy subjects [7]. Whether AO subjects develop adverse cardiac and vascular remodeling has not been investigated so far.

The aim of the present study is to assess whether changes in cardiac and arterial remodeling can be detected at an early stage in AO subjects and otherwise healthy and 'normotensive', and to investigate the contribution of blood pressure (BP) and myocardial fibrosis turnover to such potential changes.

METHODS

Subjects' selection

Caucasian subjects with AO [waist circumference >94cm for males, >80cm for females [2]] aged 40 to 65 and age-gender matched healthy volunteers without AO and body mass index <25 kg/m^2 were consecutively recruited. Subjects with diabetes (taking anti-diabetic agents or screening visit fasting glucose: >7 mmol/L), hypertension (on anti-hypertensive therapy or BP: >140/90 mmHg at the screening visit or the enrollment visit), body mass index >40 kg/m^2, history of cardiovascular, endocrine, inflammatory or malignant diseases were excluded. The study complied with the Declaration of Helsinki [8]. Written informed consent was obtained for all subjects. Local Ethics Committee approved the study. No clinical trials.gov number was assigned to this study since it started before July 1, 2005.

Metabolic phenotyping

Blood was sampled between 8 and 10 am after maintaining a supine position for 30 minutes and the following were assessed: fasting glucose, oral glucose tolerance test (to exclude diabetic patients), glycated hemoglobin, serum creatinine [estimated glomerular filtration rate by the MDRD formula [9]], ultra-sensitive C-reactive protein, alanine aminotransferase (ALT), lipid profile, leptin and adiponectin (R&D Systems, Minneapolis, MN, USA).

Body composition was estimated from the attenuation of X-rays pulsed synchronously between 40 and 100 keV using a LUNARs DPX-IQ system (LUNARs Corporation, Madison, WI, USA) [10].

Cardiac phenotyping

Left ventricular (LV) diastolic function was assessed with transthoracic doppler echocardiography (HDI 5000), with measurements of peak E wave, peak A wave, E/A ratio, deceleration time of E wave; together with doppler tissue imaging of the lateral part of mitral

annulus: E', A' and E/E' ratio. The European Society of Echocardiography guidelines were used to grade diastolic dysfunction [11], diagnosed if E' was less than 10 cm/s.

Cardiac magnetic resonance imaging (MRI) was performed on a 1.5-T magnet (Signa Excite, GE Medical Systems, Milwaukee, WI, USA) equipped with an 8-element phased-array surface coil. A steady-state free precession pulse sequence was used to assess LV function in contiguous short axis planes, as previously described in detail elsewhere [12]. Left ventricle end-diastolic volume, LV end-systolic volume, LV stroke volume, LV ejection fraction and LV mass were determined on the contiguous SSFP short-axis slices, using dedicated software (MASS™, Medis, The Netherlands). Left ventricle mass was determined at end-diastole, and papillary muscles and trabeculations were excluded for LV mass and LV volumes measurements [12]. Different scales were used to normalize LV mass: $height^{1.7}$ [13], $height^{2.7}$ [14], fat free mass [15]. Cardiac remodeling index (CRI), indicating concentric LV remodeling, is represented by the ratio of LV mass / LV end-diastolic volume [16]. Left ventricle hypertrophy, assessed by MRI, was defined according to Alfakih *et al.* as: women ≥ 60 g/m^2 and men ≥ 77g/m^2 [17].

Arterial phenotyping

During the screening visit as well as at beginning of the echotracking/MRI visit (about one month apart), blood pressure (Dinamap oscillometry; systolic: SBP, diastolic: DBP and mean: MBP) was measured consecutively three times. The mean of the last two readings was recorded for each series of measurements. Therefore, 4 measurements (2 last measurements of the 2 visits) were taken into account in this analysis. All were performed after an extended rest period of at least 30 minutes.

Carotid intima-media thickness (CIMT) and pulse wave velocity (PWV) were measured noninvasively as previously described [18].

Extra-cellular matrix phenotyping

Radioimmunoassay kits (Orion Diagnostica, Espoo, Finland) were used for determination of serum collagen peptide concentrations [PINP: aminoterminal propeptide of type I procollagen (reference range: 22 to 87 and 19 to 83ng/mL in men and women, respectively), PICP: C-terminal propeptide of procollagen type I (reference range: 69 to 163 ng/mL) was assayed using ELISA (Quidel Corporation, Santa Clara, USA), PIIINP: aminoterminal propeptide of type III procollagen (reference range: 2.3 to 6.4ng/mL), biomarkers of collagen synthesis; ICTP: type 1 collagen telopeptide, biomarker of collagen degradation (reference range: 3.2 to 3.5ng/mL)] as previously reported [19,20] with interassay variations <9.8%.

Statistical Analysis

All analyses were performed using SAS software 9.2 (SAS Institute, Cary, NC, USA). The two-tailed significance level was set at 5%. The sample size allowed to detect a difference ≥0.45 SD between groups with 80% power.

Between-group comparisons were carried out using the nonparametric Mann-Whitney test or the Chi-Squared test when appropriated.

Multivariate linear regressions were carried out on LV mass (g, g/m² g/kg, g/height$^{1.7}$, g/height$^{2.7}$), CRI, PWV, CIMT, E', E'<10cm/s and E/E'. Only significant covariables from the table 1 (besides AO, which may be forced) were selected using an interactive backward stepwise method. Intercorrelated variables (e.g. SBP, DBP and MBP) were tested separately in the models. Each biomarker was tested individually in separate models. The conditions of validity of the models (linearity, normality of residuals, homoscedasticity, absence of interaction and co-linearity, impact of outliers) were thoroughly verified for each model. The factors associated with diastolic dysfunction were identified using logistic regression. When

the assumption of linearity of the association between diastolic dysfunction and continuous covariable could not be met, the factor was dichotomized according to the median.

The results are presented as mean ± standard deviation (m±SD), regression coefficient or odds ratio (confidence interval 95%). A confirmatory sensitivity analysis was conducted on a subgroup of 50 AO and 50 controls patients matched on age, gender and mean blood pressure according to their propensity score.

RESULTS

One hundred and ninety two subjects were recruited. Twenty-two (11 AO) were excluded, 12 (2 AO) because of blood pressure >140/90 mmHg at the screening or enrolment visit, 4 took antihypertensive therapy and 6 were on thyroid hormone medication (6 AO). One patient could not attend the second visit. Therefore, our final study population included 169 subjects: 116 subjects in the AO group, and 53 controls.

Anthropometric and metabolic characteristics (Table 1)

Systolic BP (128±16 *vs.* 116±11mmHg, p<0.0001), DBP (77±11 *vs.* 71±6mmHg, p=0.0002) and MBP (94±12 *vs.* 86±7mmHg, p<0.0001) were significantly higher in AO subjects - although being still in the normal range - along with a higher heart rate (p<0.0001). Leptin concentrations were significantly higher in AO group than in controls (23.3±17.4 *vs.* 7.3±4.8 ng/ml, p<0.0001) and adiponectin concentrations were significantly lower in AO (3.1±2.3 *vs.* 3.9±2.6, p<0.0001).

Cardiac and arterial characteristics

Subjects with AO displayed a LV remodeling, as assessed by a significant increase in LV mass (97±25 *vs.* 84±21g, p=0.004) without reaching LV hypertrophy [17] and in CRI (0.69±0.16 *vs.* 0.60±0.10g/ml, p=0.004) mainly because of the increase in LV mass. A significant increase in PINP (p<0.0001), accompanied by a decrease in ICTP (p<0.0001) concentrations were observed in AO. PICP concentrations were higher in controls than in AO group (85.1±46.5 *vs.* 103.5±49.2ng/ml, p<0.0001). In both groups LV ejection fraction was normal (p=0.98). In the AO group, E' was significantly lower and E/E' higher than in controls (p<0.0001 and p =0.0003, respectively) (Table 2). Fifty-two AO (46%) had diastolic dysfunction (grade I-II) [11] compared to only 4% of controls. Abdominal obesity subjects with diastolic dysfunction compared to AO without diastolic dysfunction displayed a higher BP (SBP, DBP, MBP; respectively p=0.001, p<0.0001 and p<0.0001), waist circumference (p=0.004), CRI (p=0.004) (Online Table 1). In the whole population, subjects with diastolic dysfunction displayed higher LV mass (p=0.003), blood pressure (DBP, SBP, MBP; p<0.0001) and PIIINP (p=0.014).

The two groups (AO *vs.* controls) did not differ significantly in terms of arterial parameters [i.e. PWV (p=0.99), CIMT (p=0.099)]. Only 5% and 1% of the total population respectively presented significant intima-media thickening (defined as CIMT >0.90 mm) or arterial stiffness, as defined by a PWV >12 m/s [21]. Non-indexed LVM (r=0.25, p=0.003), LVM indexed on height$^{1.7}$ (r=0.21, p=0.016) and CRI (r=0.19, p=0.032) were positively correlated with PWV.

Structural and functional determinants of cardiac and arterial remodeling

In multivariate analysis, SBP [regression coefficient ± SEM: 0.38±0.10, p=0.0003), but the same was true for DBP (0.49±0.16, p=0.003) and MBP (0.57±0.15, p=0.0001) considered alternatively] was positively and independently associated with LVM (or scaled LVM as

expressed in g/kg of fat free mass, $g/m^{1.7}$, $g/m^{2.7}$, data not shown) and CRI (0.216±0.079, p=0.007 for SBP; 0.391±0.122, p=0.002 for DBP; 0.370±0.112, p=0.001 for MBP). In multivariate analysis, leptin concentrations were significantly associated with LV mass (-0.34±0.12, p=0.006) but not with cardiac remodeling index or diastolic dysfunction. Adiponectin concentrations were not found associated with LV mass, CRI or diastolic dysfunction. Abdominal obesity was independently associated with CRI (5.66 ±2.39, p=0.019) and scaled LVM ($g/m^{1.7}$, $g/m^{2.7}$, data not shown) but not with LVM, which was found associated with the body surface area. (Table 3)

In multivariate analysis, diastolic dysfunction was found positively and independently associated with PIIINP concentrations above median [≥2.6ng/ml, OR: 2.44 (1.05–5.69), p=0.038], AO [OR: 11.41(2.43–53.59), p=0.002], and BP above median [SBP≥122mmHg, OR: 3.18 (1.39–7.26), p=0.006; or DBP≥74 mmHg, OR: 5.55(2.35–13.14), p<0.0001; or MBP≥90mmHg, OR: 3.23(1.42–7.36), p=0.005] (Table 4, including DBP as a representative of the BP parameters).

In bivariate correlation analyses, waist circumference and waist/hip ratio were significantly associated with LV mass (r=0.56 and r=0.62, p<0.0001), CRI (r=0.42 and r=0.50, p<0.0001) as well as with E' wave (r=-0.50 and -0.37, respectively, p<0.0001).

Finally, considering the higher (although in the normal range) blood pressures in the AO group, a sensitivity analysis was performed in a subgroup of 50 AO and 50 controls propensity-score matched patients. Similar patterns were observed in this subgroup analysis i.e. higher LVM, CRI, and proportion of diastolic dysfunction, with however marginally significant differences (online data supplement Tables 2-3). Multivariate analyses confirmed that i) AO was associated with LVM and CRI, and diastolic dysfunction (the latter assessed by E'), ii) PIIINP was associated with diastolic dysfunction (data not shown).

DISCUSSION

Cardiac and arterial remodeling. Changes in structure and function

The main and novel finding of our study is that in asymptomatic and 'normotensive' healthy subjects with AO cardiac remodeling (consisting of an increased LV mass), as well as features of cardiac concentric remodeling, which were associated with the AO, and diastolic dysfunction are detectable (the latter associated with increased collagen type III turnover). Importantly we also examined the possible determinants of such early changes and found that, although in the 'normal range', BP was strongly associated with indices of cardiac remodeling and diastolic dysfunction in AO subjects, suggesting a synergistic effect of AO amplifying the deleterious effects of BP. Finally although we could also confirm the well-known association between cardiac remodeling (LVM and CRI) and arterial stiffness (PWV) [22], arterial structure (CIMT) and function (PWV) did not differ in AO subjects from that of controls, suggesting that among the early cardiovascular changes in AO cardiac remodeling probably precedes arterial remodeling.

In order to analyze the specific effect of AO, we have carefully selected healthy asymptomatic young-adult subjects, with no hypertension and no known cardiovascular disease. We have also excluded patients with morbid obesity.

Although in elderly and/or hypertensive patients LV hypertrophy [5], BP [23] and arterial stiffness [22] are major factors leading to diastolic dysfunction and subsequently to HF with preserved ejection fraction (HFpEF), in our AO asymptomatic subjects we could show that increased LV mass and diastolic dysfunction could be detected early, before LV hypertrophy, hypertension and arterial stiffening can be diagnosed.

Furthermore increased collagen type III turnover was observed in the study participants with diastolic dysfunction. We also investigated the relationship between LV geometrical remodeling, LV function and markers of myocardial collagen fibrosis indicating cardiac extracellular matrix remodeling. Irrespective from the study group we were able to identify that collagen type III turnover was positively associated with diastolic dysfunction.

Our finding is novel but consistent with our previous report of increased PIIINP in asymptomatic obese subjects [7]. In such subjects, we had previously reported that PIIINP was independently associated with insulin resistance [7], which is a common state in AO and could contribute specifically to increase myocardial fibrosis. Our results further suggest that enhanced collagen type III turnover is associated with early diastolic dysfunction independently from the adipokine pathways (the latter associated with LVM but not with diastolic dysfunction). In our previous report in obese healthy subjects [7], PIIINP and E/A ratio were significantly positively correlated. The transformation of the extracellular matrix into a more substantial collagen component, potentiated by the increase in LV mass, may alter ventricular filling, possibly contributing to the development of LV diastolic dysfunction in subjects with AO. Consistently in hypertensive patients, Martos *et al.* showed that ICTP, PICP and PIIINP concentrations were higher in patients with symptomatic HFpEF [24]. These findings in various categories of subjects suggest that PIIINP, which predict outcome in HFpEF [25,26] - though not after adjusting for other predictors [26], could be also a very early biomarker of LV diastolic dysfunction.

Blood pressure and abdominal obesity as therapeutic targets to prevent adverse cardiac remodeling?

Subjects with AO had higher SBP, DBP or MBP than controls whilst remaining within the 'normal range' and as such not currently eligible for an antihypertensive treatment. Systolic,

diastolic and mean BP above median were positively associated with changes in cardiac structure (LV mass, scaled LV mass and CRI). Furthermore, patients with BP above median (SBP≥122 mmHg, DBP≥74 mmHg, MBP≥90mmHg) had a three to five-fold increase in the rate of diastolic dysfunction.

While it has already been repeatedly demonstrated that hypertension, via LV hypertrophy and arterial stiffness, leads to diastolic dysfunction, this is the first instance, to our knowledge, demonstrating that BP within the 'normal range' is shown as a determinant of diastolic dysfunction. Law *et al.* [27] emphasized the key role of BP reduction in everyone in order to prevent cardiovascular diseases in the setting of the largest meta-analysis of randomized trials on hypertension management. Lowering SBP (by 10 mmHg) or DBP (by 5 mmHg) using any of the main classes of BP lowering drugs, reduced cardiovascular events (25% for HF) regardless of BP level before treatment. Our data suggest that an 'aggressive' and early management to reduce BP could possibly prevent cardiac structural and functional remodeling in subjects with AO.

Furthermore, that AO was independently associated with the cardiac structural (scaled LVM and CRI) and functional (diastolic dysfunction) remodeling (both in multivariate analyses led within the whole study population and after further adjustment based on propensity-score matching on age, gender and mean blood pressure in a sensitivity analysis) suggest that lifestyle changes leading to weight loss with reduction of waist circumference, independently from the use of BP lowering drugs could be a combination of paramount importance to achieve HF prevention in AO subjects. Accordingly, in a general population, a waist circumference reduction was found associated with a lower risk to develop hypertension [28].

STUDY LIMITATIONS

Our study presents certain limitations. Indeed, this study is a cross-sectional study, which prohibits from inferring a causative link. Our results may not apply to patients with morbid obesity, which were not included herein. There is no consensus for normalization of LV mass by different types of scaling (height, fat free mass, body surface area, …) and parameters used are different according to echocardiography or MRI methods. However, our findings concerning LV remodeling were consistent throughout the different definitions used for LV mass scaling. Blood pressure status of our patients was only analyzed by office BPs, although several standardized measurements were performed at each given visit. Circulating collagen peptides are not specific to cardiac tissue but previous histological studies observed a significant correlation between collagen peptides serum concentrations and cardiac fibrosis. Circulating collagen peptides are therefore an acceptable surrogate to evaluate cardiac fibrosis turnover. Of note, in the present study, no study participant exhibited abnormal ALT concentrations (data not shown), therefore ruling out the potential confounding effect of non-alcoholic fatty liver disease - which was probably absent in our study population – on PIIINP concentrations. Finally, no gadolinium-tracer was injected and thereby, myocardial fibrosis could not be assessed *in situ*.

CONCLUSIONS

'Normotensive' subjects with abdominal obesity, but otherwise asymptomatic and healthy, exhibit early detectable features of cardiac concentric remodeling as well as of enhanced collagen type III turnover associated with diastolic dysfunction, without arterial changes. These alterations may help identifying subjects with AO at higher risk for developing HF with preserved EF and who could potentially benefit from early preventive interventions, such as BP lowering- even in 'normotensive' subjects- and weight loss.

ACKNOWLEDGMENTS

We thank Mr. Pierre Pothier for the editing of this manuscript.

FUNDING SOURCES

This work was supported by French «Programme Hospitalier de Recherche Clinique», Inserm; the Région Lorraine; the «Programme National de Recherche Cardiovasculaire», the «Société Française d'Hypertension artérielle»; the «Fédération Française de Cardiologie» ; the 7th EU-FP MEDIA project (261409) and HOMAGE (305507) projects.

DISCLOSURES

None.

REFERENCES

1. Hu G, Jousilahti P, Antikainen R, Katzmarzyk PT, Tuomilehto J. Joint Effects of Physical Activity, Body Mass Index, Waist Circumference, and Waist-to-Hip Ratio on the Risk of Heart Failure. *Circulation*. 2010; 121:237 –244.

2. Holt RIG. International Diabetes Federation re-defines the metabolic syndrome. *Diabetes Obes Metab*. 2005; 7:618–620.

3. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J. Am. Coll. Cardiol*. 2005; 46:e1–82.

4. Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N. Engl. J. Med*. 2002; 347:305–313.

5. Janicki JS, Brower GL, Gardner JD, Chancey AL, Stewart JA Jr. The dynamic interaction between matrix metalloproteinase activity and adverse myocardial remodeling. *Heart Fail Rev*. 2004; 9:33–42.

6. Alla F, Kearney-Schwartz A, Radauceanu A, Das Dores S, Dousset B, Zannad F. Early changes in serum markers of cardiac extra-cellular matrix turnover in patients with uncomplicated hypertension and type II diabetes. *Eur. J. Heart Fail*. 2006; 8:147–153.

7. Quilliot D, Alla F, Böhme P, Bruntz J-F, Hammadi M, Dousset B, Ziegler O, Zannad F. Myocardial collagen turnover in normotensive obese patients: relation to insulin resistance. *Int J Obes (Lond)*. 2005; 29:1321–1328.

8. RICKHAM PP. HUMAN EXPERIMENTATION. CODE OF ETHICS OF THE WORLD MEDICAL ASSOCIATION. DECLARATION OF HELSINKI. *Br Med J*. 1964; 2:177.

9. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann. Intern. Med.* 2003; 139:137–147.

10. He M, Tan KC, Li ET, Kung AW. Body fat determination by dual energy X-ray absorptiometry and its relation to body mass index and waist circumference in Hong Kong Chinese. *Int. J. Obes. Relat. Metab. Disord*. 2001; 25:748–752.

11. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelisa A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr*. 2009; 10:165–193.

12. Mandry D, Lapicque F, Odille F, Djaballah W, Codreanu A, Escanyé J-M, Felblinger J, Karcher G, Claudon M, Marie P-Y. Multicompartmental analysis of late contrast enhancement in areas of myocardial infarction supplied by chronically occluded coronary arteries. *J Magn Reson Imaging*. 2009; 29:78–85.

13. Chirinos JA, Segers P, De Buyzere ML, Kronmal RA, Raja MW, De Bacquer D, Claessens T, Gillebert TC, St John-Sutton M, Rietzschel ER. Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. *Hypertension*. 2010; 56:91–98.

14. de Simone G, Izzo R, Trimarco B. Left ventricular hypertrophy: old marker, new problems and new possibilities. *J. Hypertens.* 2011; 29:1480–1482.

15. Bella JN, Devereux RB, Roman MJ, O'Grady MJ, Welty TK, Lee ET, Fabsitz RR, Howard BV. Relations of left ventricular mass to fat-free and adipose body mass: the strong heart study. The Strong Heart Study Investigators. *Circulation*. 1998; 98:2538–2544.

16. Bluemke DA, Kronmal RA, Lima JAC, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J. Am. Coll. Cardiol*. 2008; 52:2148–2155.

17. Alfakih K, Plein S, Bloomer T, Jones T, Ridgway J, Sivananthan M. Comparison of right ventricular volume measurements between axial and short axis orientation using steady-state free precession magnetic resonance imaging. *J Magn Reson Imaging*. 2003; 18:25–32.

18. Kearney-Schwartz A, Rossignol P, Bracard S, Felblinger J, Fay R, Boivin J-M, Lecompte T, Lacolley P, Benetos A, Zannad F. Vascular structure and function is correlated to cognitive performance and white matter hyperintensities in older hypertensive patients with subjective memory complaints. *Stroke*. 2009; 40:1229–1236.

19. Zannad F, Rossignol P, Iraqi W. Extracellular matrix fibrotic markers in heart failure. *Heart Fail Rev*. 2010; 15:319–329.

20. Iraqi W, Rossignol P, Angioi M, Fay R, Nuée J, Ketelslegers JM, Vincent J, Pitt B, Zannad F. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. *Circulation*. 2009; 119:2471–2479.

21. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, Grassi G, Heagerty AM, Kjeldsen SE, Laurent S, Narkiewicz K, Ruilope L, Rynkiewicz A, Schmieder RE, Struijker Boudier HAJ, Zanchetti A, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Kjeldsen SE, Erdine S, Narkiewicz K, Kiowski W, Agabiti-Rosei E, Ambrosioni E, Cifkova R, Dominiczak A, Fagard R, Heagerty AM, Laurent S, Lindholm LH, Mancia G, Manolis A, Nilsson PM, Redon J, Schmieder RE, Struijker-Boudier HAJ, Viigimaa M, Filippatos G, Adamopoulos S, Agabiti-Rosei E, Ambrosioni E, Bertomeu V, Clement D, Erdine S, Farsang C, Gaita D, Kiowski W, Lip G, Mallion J-M, Manolis AJ, Nilsson PM, O'Brien E, Ponikowski P, Redon J, Ruschitzka F, Tamargo J, van Zwieten P, Viigimaa M, Waeber B, Williams B, Zamorano JL, The task force for the management of arterial hypertension of the European Society of Hypertension, The task force for the management of arterial hypertension of the European Society of Cardiology. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur. Heart J*. 2007; 28:1462–1536.

22. Kang S, Fan H-M, Li J, Fan L-Y, Miao A-Y, Bao Y, Wu L-Z, Zhu Y, Zhang D-F, Liu Z-M. Relationship of arterial stiffness and early mild diastolic heart failure in general middle and aged population. *Eur. Heart J*. 2010; 31:2799–2807.

23. Wright JW, Mizutani S, Harding JW. Pathways involved in the transition from hypertension to hypertrophy to heart failure. Treatment strategies. *Heart Fail Rev*. 2008; 13:367–375.

24. Martos R, Baugh J, Ledwidge M, O'Loughlin C, Conlon C, Patle A, Donnelly SC, McDonald K. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. *Circulation*. 2007; 115:888–895.

25. Barasch E, Gottdiener JS, Aurigemma G, Kitzman DW, Han J, Kop WJ, Tracy RP. The relationship between serum markers of collagen turnover and cardiovascular outcome in the elderly: the Cardiovascular Health Study. *Circ Heart Fail*. 2011; 4:733–739.

26. Krum H, Elsik M, Schneider HG, Ptaszynska A, Black M, Carson PE, Komajda M, Massie BM, McKelvie RS, McMurray JJ, Zile MR, Anand IS. Relation of peripheral collagen markers to death and hospitalization in patients with heart failure and preserved ejection fraction: results of the I-PRESERVE collagen substudy. *Circ Heart Fail*. 2011; 4:561–568.

27. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009; 338:b1665.

28. Luo W, Guo Z, Hu X, Zhou Z, Mingwu, Zhang L, Liu J. A prospective study on association between 2years change of waist circumference and incident hypertension in Han Chinese. *Int. J. Cardiol.* [Internet]. 2012 [cited 2012 Aug 11];Available from: http://www.ncbi.nlm.nih.gov/pubmed/22871264

TABLE 1: Anthropometric and metabolic characteristics of the study population

	Abdominal obesity (AO) group		**Control group**		**p ***
	n		**n**		
Anthropometric and metabolic characteristics					
Gender M/F	116	58/58	53	24/29	0.57
Age (years)	116	55 ± 6	53	54 ± 6	0.18
BMI (kg/m²)	116	31.7 ± 3.4	53	22.4 ± 2.0	< 0.0001
Body surface area (m^2)	116	2.07 ± 0.18	53	1.73 ± 0.14	< 0.0001
Waist circumference (cm)	116	103 ± 10	53	78 ± 8	< 0.0001
Waist / hip ratio	116	0.94 ± 0.10	53	0.82 ± 0.09	< 0.0001
Mean SBP (mmHg)	116	128 ± 16	53	116 ± 11	< 0.0001
Mean DBP (mmHg)	116	77 ± 11	53	71 ± 6	0.0002
Mean MBP (mmHg)	116	94 ± 12	53	86 ± 7	< 0.0001
Mean HR (bpm)	116	70 ± 11	53	62 ± 8	< 0.0001
Triglycerides (mmol/l)	116	1.62 ± 1.16	53	0.88 ± 0.43	< 0.0001
Total cholesterol (mmol/l)	116	5.78 ± 0.99	53	5.44 ± 0.83	0.045
HDL Cholesterol (mmol/l)	116	1.42 ± 0.38	53	1.60 ± 0.36	0.002
LDL Cholesterol (mmol/l)	116	3.63 ± 0.88	53	3.45 ± 0.73	0.19
Leptin (ng/ml)	116	23.3 ± 17.4	53	7.3 ± 4.8	<0.0001
Adiponectin (µg/ml)	116	3.1 ± 2.3	53	3.9 ± 2.6	<0.0001
Fasting glucose (mmol/l)	112	5.18 ± 0.95	49	4.93 ± 0.46	0.16
Glycated hemoglobin	113	5.8 ± 0.5	50	5.6 ± 0.3	0.020

(%)					
CRP (mg/l)	115	3.7 ± 5.5	52	1.2 ± 1.3	< 0.0001
Protidemia (g/l)	116	72 ± 4	52	69 ± 4	< 0.0001
eGFR (MDRD, ml/min/1.73m^2)	116	76 ± 10	53	77 ± 12	0.92

BMI: body mass index, CRP: C reactive protein, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, F: female, HDL: High density lipoprotein, HR: heart rate, bpm: beats per minute, LDL: Low density lipoprotein, M: male, MBP: mean blood pressure, MDRD: Modification in Diet Renal Disease, SBP: systolic blood pressure.

* p-values from the Mann-Whitney or Chi-Squared test as appropriated.

TABLE 2: Cardiac and arterial characteristics of the study population

	Abdominal obesity (AO) group		**Control group**		**p ***
	n		**n**		
Cardiac characteristics					
PINP (ng/ml)	115	36 ± 16	53	22 ± 14	< 0.0001
PICP (ng/ml)	116	85.1 ± 46.5	55	103.5 ± 49.2	<0.0001
PIIINP (ng/ml)	110	2.6 ± 1.3	53	3.4 ± 6.7	0.084
ICTP (ng/ml)	115	3.9 ± 1.0	53	4.6 ± 0.9	< 0.0001
LVM (g) †	93	97 ± 25	47	84 ± 21	0.004
LVMi (g/m²)	93	47 ± 10	47	48 ± 10	0.21
LVM FFM (DEXA, g/kg)	93	1.79 ± 0.28	47	1.78 ± 0.28	0.86
LVM (g/height^1.7)	93	40.1 ± 8.2	47	34.7 ± 7.3	< 0.0001
LVM (g/height^2.7)	93	24.0 ± 4.5	47	20.6 ± 4.1	< 0.0001
LVEF (%) †	93	60 ± 6	47	59 ± 7	0.98
LVEDV (ml) †	93	142 ± 29	47	141 ± 25	0.90
LVESV (ml) †	93	58 ± 19	47	57 ± 15	0.93
LVEV (ml) †	93	84 ± 15	47	84 ± 17	0.83
CO = LVEV x HR (l/min)	93	5.99 ± 1.30	47	5.50 ± 1.03	0.056
CRI = LVM/LVEDV (g/ml)	93	0.69 ± 0.16	47	0.60 ± 0.10	0.004
E (cm/s) ‡	116	66 ± 16	52	74 ± 15	0.005
A (cm/s) ‡	116	60 ± 15	52	53 ± 10	0.002
E/A ‡	116	1.13 ± 0.31	52	1.41 ± 0.31	< 0.0001
E' (cm/s) ‡	112	10.4 ± 2.5	52	13.7 ± 2.5	< 0.0001
A' (cm/s) ‡	113	11.0 ± 2.6	52	9.4 ± 2.6	0.0002

E/E' ‡	113	6.6 ± 1.7	52	5.5 ± 1.5	0.0003

Arterial characteristics

PWV (m/s)	95	8.08 ± 1.6	48	8.0 ± 1.4	0.99
IMT (mm)	97	0.66 ± 0.15	48	0.61 ± 0.12	0.099

CO: cardiac output, CRI: cardiac remodeling index, ICTP: type 1 collagen telopeptide, IMT : intima-media thickness, LVEDV: LV end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: LV end-systolic volume, LVEV: LV ejection volume, LVM: left ventricular mass, M: male, LVM FFM: LVM indexed by fat free mass, LVMi: LVM indexed by BSA (Boyd), $LVM_{height^{\sim}1.7}$: LVM indexed by height^2.7, $LVM_{height^{\sim}2.7}$: LVM indexed by height^2.7, MBP: mean blood pressure, MDRD: Modification in Diet Renal Disease, PICP: carboxyterminal propeptide of type I procollagen, PINP: aminoterminal propeptide of type I procollagen, PIIINP aminoterminal propeptide of type III procollagen, PWV : pulse wave velocity, SBP: systolic blood pressure,

* p-values from the Mann-Whitney test.

† Assessed by cardiac magnetic resonance imaging

‡ Assessed by transthoracic echocardiography

TABLE 3: Factors associated with left ventricular mass and cardiac remodeling index in multivariate analysis.

LVM (g)				
	Covariable	Regression coefficient ± SEM	p-value	Variance explained (%)*
	AO (yes vs. no)	-2.92 ± 4.36	0.50	0.1%
	FG (yes vs. no)	-14.4 ± 4.47	0.017	2.9%
	BSA (m^2)	46.7 ± 11.3	<0.0001	4.9%
	SBP (mmHg)	0.38 ± 0.10	0..0003	4.0%
	Leptin (ng/ml)	-0.34 ± 0.12	0.006	2.3%
CRI (10² g/ml)				
	Covariable	Regression coefficient ± SEM	p-value	Variance explained (%)*
	AO (yes vs. no)	5.66 ± 2.39	0.019	2.8%
	FG (yes vs. no)	-11.8 ± 2.15	<0.0001	15.2%
	SBP (mmHg)	0.216 ± 0.079	0.007	3.7%

AO: Abdominal obesity, BSA: body surface area, CRI: cardiac remodeling index, FG: Female gender, LVM: Left ventricular mass, SBP: systolic blood pressure, p: p-values from logistic regression

* Independently of other factor

TABLE 4: Factors associated with diastolic dysfunction in multivariate analysis.

DD			
	Covariable	OR (95% CI)	p-value
	AO (yes vs. no)	11.41 (2.43 – 53.59)	0.002
	PIIINP ≥ 2.6 ng/ml (yes vs. no)	2.44 (1.05 - 5.69)	0.038
	TG > 1.11 mmol/l	2.77 (1.14 – 6.76)	0.025
	DBP ≥ 74 mmHg	5.55 (2.35 - 13.14)	<0.0001

AO: Abdominal obesity, DD: diastolic dysfunction, PIIINP aminoterminal propeptide of type III procollagen, SBP: systolic blood pressure, TG: triglycerides,

* OR (95%CI): odds ratio (95% confidence interval); p: p-values from logistic regression.

ONLINE SUPPLEMENT TABLES

ONLINE TABLE 1: Characteristics according to diastolic dysfunction in AO subjects only (E' < 10 cm/s) (sensitivity analysis)

	Diastolic dysfunction group		Control group		p
	n		n		
Clinical characteristics					
Gender M/F	52	33/19 (63% M)	61	22/39 (36% M)	0.004
Age (years)	52	57 ± 5	61	54 ± 6	0.026
BMI (kg/m^2)	52	32.2 ± 3.1	61	31.4 ± 3.7	0.13
Body surface area (m^2)	52	2.11 ± 0.17	61	2.04 ± 0.19	0.035
Waist circumference (cm)	52	106 ± 9	61	101 ± 11	0.004
Waist / hip ratio	52	0.97 ± 0.08	61	0.92 ± 0.11	0.004
Mean SBP (mmHg)	52	134 ± 16	61	124 ± 14	0.001
Mean DBP (mmHg)	52	81 ± 12	61	72 ± 8	< 0.0001
Mean MBP (mmHg)	52	99 ± 12	61	90 ± 9	< 0.0001
Mean HR (bpm)	52	71 ± 10	61	69 ± 11	0.19
Biological characteristics					
Triglycerides (mmol/l)	52	1.99 ± 1.52	61	1.29 ± 0.60	0.0006
Total cholesterol (mmol/l)	52	5.81 ± 0.98	61	5.78 ± 1.02	0.89
HDL Cholesterol (mmol/l)	52	1.32 ± 0.33	61	1.51 ± 0.41	0.013
LDL Cholesterol (mmol/l)	52	3.59 ± 0.87	61	3.68 ± 0.91	0.8
Fasting glucose (mmol/l)	50	5.29 ± 0.71	59	5.09 ± 1.12	0.021
Glycated hemoglobin (%)	51	5.8 ± 0.4	59	5.7 ± 0.6	0.25
CRP (mg/l)	52	4.4 ± 6.8	61	3.2 ± 4.3	0.16
Protidemia (g/l)	51	73 ± 4	60	71 ± 4	0.044
eGFR (MDRD,	52	77 ± 9	61	75 ± 11	0.22

ml/min/1.73m^2)					
PINP (ng/ml)	52	39 ± 17	60	33 ± 16	0.051
PIIINP (ng/ml)	48	2.7 ± 1.1	59	2.4 ± 1.5	0.18
ICTP (ng/ml)	51	3.9 ± 1.2	61	3.9 ± 0.9	0.78
Cardiac phenotyping					
LVM (g)*	40	103 ± 28	51	92 ± 22	0.053
LVMi (g/m^2)*	40	49 ± 11	51	45 ± 9	0.077
LVM FFM (DEXA, g/kg)*	40	1.80 ± 0.30	51	1.80 ± 0.27	0.77
LVEF (%)*	40	58 ± 6	51	61 ± 7	0.004
LVEDV (ml)*	40	139 ± 28	51	145 ± 29	0.64
LVESV (ml)*	40	59 ± 16	51	57 ± 21	0.27
LVEV (ml)*	40	80 ± 15	51	87 ± 14	0.039
CRI = LVM/LVEDV (g/ml)*	40	0.75 ± 0.18	51	0.64 ± 0.12	0.004
E (cm/s) †	52	60 ± 12	61	73 ± 17	< 0.0001
A (cm/s) †	52	63 ± 13	61	60 ± 16	0.19
E/A†	52	0.98 ± 0.23	61	1.26 ± 0.29	< 0.0001
E' (cm/s) †	52	8.3 ± 1.1	61	12.3 ± 1.8	< 0.0001
A' (cm/s) †	52	11.1 ± 2.6	61	10.9 ± 2.6	0.83
E/E'†	52	7.3 ± 1.8	61	6.0 ± 1.5	< 0.0001
Vascular phenotyping					
PWV (m/s)	40	8.1 ± 1.5	51	7.9 ± 1.6	0.21
IMT (mm)	42	0.67 ± 0.14	52	0.64 ± 0.15	0.14

BMI: body mass index, CO: cardiac output, CRI: cardiac remodeling index, CRP: C reactive protein, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, F: female, HDL: High density lipoprotein, HR: heart rate, bpm: beats per minute, ICTP: type 1 collagen telopeptide, IMT : intima-media thickness, LDL: Low density lipoprotein, LVEDV: LV end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: LV end-systolic volume, LVEV: LV ejection volume, LVM: left ventricular mass, LVM FFM: LVM indexed by fat free mass, LVMi: LVM indexed by BSA (Boyd), M: male, MBP: mean blood pressure, MDRD: Modification in Diet Renal Disease, PINP: aminoterminal propeptide of type I procollagen, PIIINP aminoterminal propeptide of type III procollagen, PWV : pulse wave velocity, SBP: systolic blood pressure,

* Assessed by cardiac magnetic resonance imaging

† Assessed by Transthoracic echocardiography

ONLINE TABLE 2: Anthropometric and metabolic characteristics of the study population (sensitivity analysis)

	Abdominal obesity		**Matched controls**		**p-value***
Age (years)	50	53.7 ± 6.2	50	53.9 ± 5.9	0.98
Female gender	50	29 (58%)	50	28 (56%)	0.84
Fat-free mass (kg)	50	53.0 ± 10.6	50	47.4 ± 8.8	0.005
SBP (mmHg)	50	118 ± 10	50	116 ± 11	0.61
DBP (mmHg)	50	71 ± 7	50	72 ± 6	0.65
MBP (mmHg)	50	87 ± 7	50	87 ± 7	0.88
Leptin (ng/ml)	50	26.55 ± 18.43	50	7.22 ± 4.53	<0.0001
Adiponectin (µg/ml)	50	3.44 ± 2.32	50	3.73 ± 2.49	0.64

BMI: body mass index, CRP: C reactive protein, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, F: female, HDL: High-density lipoprotein, HR: heart rate, bpm: beats per minute, LDL: Low density lipoprotein, M: male, MBP: mean blood pressure, MDRD: Modification in Diet Renal Disease, SBP: systolic blood pressure.

* p-values from the Mann-Whitney or Chi-Squared test as appropriated.

ONLINE TABLE 3: Cardiac and arterial characteristics of the study population (sensitivity analysis)

	Abdominal obesity (AO) group		Control group		p *
	n		n		
Cardiac characteristics					
PINP (ng/ml)	50	35.0 ± 16.7	50	22.1 ± 14.5	0.0003
PICP (ng/ml)	50	91 ± 63	50	103 ± 49	0.007
PIIINP (ng/ml)	45	2.43 ± 1.48	50	3.33 ± 6.84	0.27
ICTP (ng/ml)	50	3.80 ± 0.97	50	4.53 ± 0.86	0.0001
LVM (g) †	42	92 ± 23	44	84 ± 22	0.096
LVM (g/height^2.7)	42	23.3 ± 3.7	44	20.7 ± 4.2	0.001
LVEDV (ml) †	42	141 ± 31	44	140 ± 26	0.81
CRI = LVM/LVEDV (g/ml)	42	0.66 ± 0.15	44	0.60 ± 0.11	0.14
Diastolic dysfunction (E' < 10 m/s)	50	17 (34%)	49	2 (4%)	0.0004

CO: cardiac output, CRI: cardiac remodeling index, ICTP: type 1 collagen telopeptide, IMT : intima-media thickness, LVEDV: LV end-diastolic volume, LVEF: left ventricular ejection fraction, LVESV: LV end-systolic volume, LVEV: LV ejection volume, LVM: left ventricular mass, M: male, LVM FFM: LVM indexed by fat free mass, LVMi: LVM indexed by BSA (Boyd), $LVM_{height^{-1.7}}$: LVM indexed by height^2.7, $LVM_{height^{-2.7}}$: LVM indexed by height^2.7, MBP: mean blood pressure, MDRD: Modification in Diet Renal Disease, PICP: carboxyterminal propeptide of type I procollagen, PINP: aminoterminal propeptide of type I procollagen, PIIINP aminoterminal propeptide of type III procollagen, PWV : pulse wave velocity, SBP: systolic blood pressure.

* p-values from the Mann-Whitney test.

† Assessed by cardiac magnetic resonance imaging

‡ Assessed by transthoracic echocardiography

4.1.2 *Comprehensive MRI analysis of early cardiac and vascular remodeling in middle-aged patients with abdominal obesity*

Damien Mandry, Romain Eschalier, Anna Kearney-Schwartz, Patrick Rossignol, Laure Joly, Wassila Djaballah, Philip Bohme, Jean M. Escanye, Pierre A. Vuissoz, Renaud Fay, Faïez Zannad, and Pierre Y. Marie

Ce travail a fait l'objet d'une publication[205] dans "Journal of Hypertension".

Objectifs. Evaluer par l'utilisation de l'imagerie par résonnance magnétique cardiaque la prévalence d'un remodelage ventriculaire gauche chez des patients d'âge moyen présentant une obésité abdominale. Les remodelages ventriculaires gauche et artériels sont habituellement associés avec l'hypertension artérielle, mais peu de travaux ont été réalisés chez des patients porteurs d'obésité abdominale (population à haut risque cardiovasculaire et de développement d'hypertension artérielle et de syndrome métabolique).

Méthodes. 70 sujets d'âge moyen porteur d'obésité abdominale (56 ± 5 ans, 49% de femme, 69% avec un IMC > 30kg/m^2), sans autre facteur de risque cardiovasculaire (16% de patients non traités au stade 1 d'hypertension artérielle), et 40 sujets contrôles ont bénéficié d'IRM à la recherche d'un remodelage cardiaque concentrique (ratio masse ventriculaire gauche / volume télé-diastolique augmenté) et d'identifier des déterminants potentiels de cet état comme les indexes de compliance artérielle [vitesse d'onde de pouls aortique et compliance totale artérielle (TAC)] et les résistances vasculaires périphériques totales (TVPR).

Résultats. 20 sujets avec obésité abdominale (29%) présentent un remodelage ventriculaire gauche concentrique (CR+). Les sujets CR+ sont principalement des hommes (85%), fréquemment au stade 1 d'hypertension artérielle (45%) et certains présentent une hypertrophie ventriculaire gauche (20%). Après ajustement par le sexe, nous retrouvons une diminution progressive de la TAC entre les sujets contrôles (mean ± SEM : 2.10 ± 0.06 ml/mmHg), CR- (1.82 ± 0.06 ml/mmHg) et CR+ (1.42 ± 0.09 ml/mmHg, $p<0.005$). De plus

les TVPRs sont plus basses chez les sujets CR- que les contrôles (14.7 ± 0.5 vs. 16.8 ± 0.5 ml/mmHg, p=0.005).

Conclusions. Un remodelage ventriculaire gauche est fréquemment mis en évidence par IRM chez des sujets asymptomatiques présentant une obésité abdominale. Ce remodelage est associé à une diminution de la compliance artérielle non contre-balancée par une diminution des résistances périphériques vasculaires totales, suggérant un remodelage vasculaire initialement proximal.

Original Article

Comprehensive MRI analysis of early cardiac and vascular remodeling in middle-aged patients with abdominal obesity

Damien Mandry[a,b,c], Romain Eschalier[c,d], Anna Kearney-Schwartz[c,d,e,f], Patrick Rossignol[c,d,e], Laure Joly[c,e,f], Wassila Djaballah[b,c,g], Philip Böhme[h], Jean M. Escanyé[c,g,i], Pierre A. Vuissoz[b,c], Renaud Fay[d], Faïez Zannad[c,d,e,j], and Pierre Y. Marie[c,e,g]

Objectives: To determine, using a comprehensive MRI investigation, prevalence and vascular correlates of early left-ventricular concentric remodeling in middle-aged patients with abdominal obesity. Left-ventricular and vascular remodeling are commonly associated with hypertension, but little is known for abdominal obesity patients, a population with definite increase in cardiovascular risk and high rates of further developments of hypertension and of the metabolic syndrome.

Methods: Seventy middle-aged abdominal obesity patients (56 ± 5 years, 49% women, 69% with body mass index $> 30\,kg/m^2$), who had no additional cardiovascular risk factor except for untreated stage 1 hypertension (16%), and 40 controls underwent MRI for detecting concentric remodeling (increase in left-ventricular mass/end-diastolic volume ratio) and identifying potential determinants, including arterial compliance indexes [aortic pulse wave velocity and total arterial compliance (TAC)] and total peripheral vascular resistances (TPVRs).

Results: Twenty abdominal obesity patients (29%) had concentric remodeling (concentric remodeling+), whereas 50 did not (concentric remodeling−). Concentric remodeling+ patients were mostly men (85%), they frequently had stage 1 hypertension (45%) and few had left-ventricular hypertrophy (20%). When adjusted for sex, there was a step-by-step decline in TAC between controls (mean ± SEM: 2.10 ± 0.06 ml/mmHg), concentric remodeling− (1.82 ± 0.06 ml/mmHg) and concentric remodeling+ (1.42 ± 0.09 ml/mmHg, $P < 0.005$ for inter-group comparisons) and TPVRs were lower than controls for concentric remodeling− (14.7 ± 0.5 vs. 16.8 ± 0.5 ml/mmHg, $P = 0.005$) but not for concentric remodeling+ (17.5 ± 0.7 mmHg/min per l).

Conclusions: Concentric remodeling is frequently documented by MRI in the middle-aged men with abdominal obesity and in association with a decrease in TAC no longer counter-balanced by a decrease in TPVR, suggesting a remodeling from proximal to peripheral vasculature.

Keywords: abdominal obesity, arterial compliance, cardiac concentric remodeling, cardiac hypertrophy, hypertension, MRI, peripheral vascular resistances

Abbreviations: BMI, body mass index; DEXA, dual-energy X-ray absorptiometry; EDV, end-diastolic volume; FFM, free-fat mass; LV, left ventricle; MRI, magnetic resonance imaging; NS, nonsignificant; PWV, pulse wave velocity; SAT, sub-cutaneous adipose tissue; TAC, total arterial compliance index; TPVR, total peripheral vascular resistance; VAT, visceral adipose tissue

INTRODUCTION

Patients with abdominal obesity exhibit a definite increase in cardiovascular risk and high rates of further developments of hypertension and of the metabolic syndrome [1–3]. However, prevalence and vascular correlates of left-ventricular remodeling are poorly known in abdominal obesity patients.

Left-ventricular remodeling is primarily concentric under pressure overload and a very high frequency of left-ventricular concentric remodeling was recently documented in general obesity and when using the criterion of an increase in the left-ventricular mass/end-diastolic ratio at MRI [4–6]. This ratio was additionally associated with an increased cardiovascular risk in more general populations, especially when present early in life [7,8] and similarly to that documented for concentric remodeling detected by echocardiography [9–12].

In addition, the relationship between concentric remodeling and the remodeling of proximal to peripheral vasculature remains to be clarified in abdominal obesity patients. On one hand, peripheral vascular resistances are

Journal of Hypertension 2012, 30:000–000

[a]CHU-Nancy, Department of Radiology, [b]INSERM, U947, [c]Nancy-Université, [d]INSERM, Centre d'Investigation Clinique CIC-P 9501, [e]INSERM, U961, [f]CHU-Nancy, Department of Geriatric Medicine, [g]CHU-Nancy, Department of Nuclear Medicine, [h]CHU-Nancy, Department of Diabetology and Nutrition, [i]CNRS, FRE 2415 and [j]CHU-Nancy, Department of Cardiology, Nancy, France

Correspondence to Professor Pierre-Yves Marie, CHU-Nancy, Hôpitaux de BRABOIS, Service de Médecine Nucléaire, Allée du Morvan, 54500 Vandœuvre, France. Tel: +33 383153911; fax: +33 383153838; e-mail: py.marie@chu-nancy.fr

Received 29 June 2011 **Revised** 9 November 2011 **Accepted** 18 November 2011

J Hypertens 30:000–000

DOI:10.1097/HJH.0b013e32834f6f3f

usually decreased in uncomplicated obesity, fat tissue constituting a low-resistance circulatory compartment [13], and this decrease should normally act against the development of left-ventricular hypertrophy and concentric remodeling.

On the other hand, a decrease in the compliance of great arteries is commonly documented in general obesity [4,14–17] and it might be one of the mechanisms of obesity-related concentric remodeling. In particular, this decrease is known to play a role in the development of LV hypertrophy through deleterious changes in reflection waves [18,19] and it is strongly linked to the concentric remodeling of hypertensive patients [20,21].

By using a comprehensive MRI investigation, in which the ratio of left-ventricular mass/end-diastolic volume and indexes of vascular function could be measured precisely, the present study aimed to determine the prevalence of concentric remodeling in middle-aged patients with abdominal obesity and relationships with vascular remodeling.

METHODS

Patient selection and study organization

The study protocol was approved by the local Ethics Committee and all study participants gave signed informed consent to participate. Abdominal obesity patients and a control group of nonobese healthy volunteers, with an age between 40 and 65 years, were prospectively recruited by press advertisement and were ultimately included following a preselection medical assessment, associating clinical examination with one blood pressure measurement after at least a 10 min resting period, ECG recording and blood sampling. The final selection for the present analysis was based in the abdominal obesity group, on the presence of a definite abdominal obesity with waist circumference greater than 102 cm for men and greater than 88 cm for women [3] and the absence of morbid obesity [i.e. body mass index (BMI) > 40 kg/m^2) and in controls, by a waist circumference less than 94 cm for men and less than 80 cm for women, in order to exclude any central obesity [22].

Exclusion criteria were: any history of cardiovascular disease and any medical treatment with cardiovascular effect, diabetes according to American Diabetes Association diagnosis definitions [23], any history of hypertension or the finding of an overt hypertension still untreated at the preselection examination (160/100 mmHg corresponding to a $>$ stage 1 hypertension [24]), inflammatory disease, renal, hepatic or pulmonary insufficiency, contra-indication to MRI, absence of sinus cardiac rhythm and women with child-bearing potential.

Patients were subsequently referred within 1 month to dual x-ray absorptiometry for the determination of body mass composition and MRI for measuring mass, volume and ejection fraction of the left ventricle (LV), abdominal visceral adipose tissue (VAT), aortic pulse wave velocity (PWV), total arterial compliance (TAC) index and total peripheral vascular resistance (TPVR).

Magnetic resonance imaging sequence recording

Magnetic resonance imaging was performed on a 1.5-T magnet (Sigma Excite; GE Medical Systems, Milwaukee, Wisconsin, USA) equipped with an eight-element phased-array surface coil. A steady-state free precession pulse sequence was used to assess left-ventricular function in contiguous short axis planes, each slice being recorded during a 15-s or less breath-hold period [25,26]. Main acquisition parameters were as follows: 8 mm slice thickness, 3.5–3.9 ms repetition time, 14–16 K-space lines per segment, 30 phases per cardiac cycle with view sharing, field-of-view ranging from 32 to 38 cm and a 224×224 matrix.

Cardiac flow was determined in ascending aorta, using a velocity-encoded phase-contrast gradient-echo sequence with a k-space segmentation of 6 lines per segment and during a 12–17-s expiratory breath-hold period. A single slice was positioned perpendicularly to the ascending aorta and acquisition parameters were as follows: 10 mm slice thickness, 15° flip angle, 3–4 ms echo time, 6–7 ms repetition time, 31 kHz bandwidth, 6 K-space lines per segment, 32 phases per cardiac cycle with view sharing, unidirectional velocity encoding with a maximal velocity set to 150 cm/s, field-of-view as small as possible between 30 and 38 cm and a 256×128 matrix.

This velocity-encoded sequence was reemployed for determining the aortic PWV during free breathing [17]. The temporal resolution was enhanced by the recording of only 1 K-space line per segment and 200 phases per cardiac cycle. Two slices separated by a distance of 15 cm were positioned perpendicularly to the descending aorta, the upper slice crossing the median portion of the ascending aorta. This allowed aortic PWV to be recorded between the median portion of the ascending aorta and a distal aortic level, under the diaphragm [17].

Abdominal VAT was determined on an axial abdominal slice positioned at the level of L3-L4 [27–29]. This slice was recorded during breath-hold with a fast-spin-echo sequence and the following parameters: 10 mm slice thickness, 62 kHz bandwidth, 12 ms echo time and 7 echo train, 480 ms repetition time, 200 ms inversion time, field-of-view of 44–48 cm, 256×190 matrix, and with water saturation in order that images contain only fat signal [30].

Systolic, diastolic and mean blood brachial pressures were measured by automated sphygmomanometer dedicated to MRI (Maglife C, Shiller Medical, Wissembourg, France). Three measurements were obtained during the MRI examination and mean values were stored for the analyses presented here.

Analyses of magnetic resonance imaging images

Left-ventricular end-diastolic volume (EDV), stroke volume, ejection fraction and left-ventricular mass were determined on the contiguous short-axis slices, using dedicated software (MASS; Medis, The Netherlands). Left-ventricular mass was determined at end-diastole, papillary muscles and trabeculations being excluded [25,26].

The velocity-encoded slices were analyzed with the dedicated 'CV flow' software in which aortic contours are detected automatically (Medis). The values of cardiac flow and of stroke volume were used to calculate the TAC index (stroke volume/pulse pressure [20,21]) and the TPVR (mean pressure/cardiac flow).

Aortic PWV (m/s) was determined by dividing arterial length by the interval time separating the onset of the pulse waves between the proximal (median ascending aorta) and distal (under the diaphragm) aortic levels [17].

The surfaces of visceral and subcutaneous adipose tissue (VAT and SAT, respectively) were determined on the abdominal fast-spin-echo slices. A conventional method was used whereby fat voxels are identified with a manual tracing of the limits between sub-cutaneous and visceral fat and a manual setting of an intensity threshold [30].

Dual-energy X-ray absorptiometry

Body composition was estimated from the attenuation of X-rays pulsed synchronously between 40 and 100 keV using a LUNARs DPX-IQ system (LUNARs Corporation, Madison, Wisconsin, USA) [30]. Fat, lean and bone masses were determined, and fat-free mass (FFM) was calculated as the sum of bone and lean masses.

Statistical analysis

For the initial comparisons between controls and abdominal obesity patients: continuous variables were expressed as mean ± standard deviation (SD) and compared using Mann–Whitney tests and discrete variables were expressed as percentages and compared with chi-squared tests or Fisher exact tests when more appropriate.

For subsequent comparisons between the three groups comprised of controls and abdominal obesity patients with or without concentric remodeling, quantitative variables were expressed as mean ± standard error of the mean (SEM) after adjustment for sex differences using ANOVA and these groups were subsequently compared using Scheffe's adjustment for multiple comparison. The log-transformation of factors exhibiting significant skewness did not change the results. Univariate correlations between quantitative variables were assessed using Spearman non-parametric tests and a P value less than 0.05 was considered to indicate a significant prediction for all tests.

Multivariate stepwise ascending regression analyses were additionally used in order to identify the best independent correlates of left-ventricular mass/end-diastolic ratio in the whole study population and among all the demographic, anthropometric, body composition and vascular parameters listed in Tables 1–3. All variables showing a P value less than 0.10 upon univariate analysis were tested. Limits of significance for entering and removing variables were 0.05 and 0.10, respectively.

RESULTS

Comparisons between abdominal obesity patients and controls

Seventy abdominal obesity patients and 40 healthy controls were ultimately considered in the analysis. Abdominal

TABLE 1. Comparison of main recorded data between the control group and the total group of patients with abdominal obesity

	Controls ($n=40$)	Abdominal obesity ($n=70$)	P value
Demographics			
Age (years)	54.8±4.5	55.8±5.4	NS
Women	19 (48%)	34 (49%)	NS
Anthropometry			
Height (cm)	169±8	168±9	NS
Weight (kg)	64±9	90±11	<0.001
Body surface area (m^2)	1.73±0.15	2.05±0.17	<0.001
BMI (kg/m^2)	22.5±2.2	32.1±3.1	<0.001
>30 kg/m^2	0 (0%)	48 (69%)	<0.001
Waist circumference (cm)	80±8	105±8	<0.001
Body composition			
Fat body mass (DEXA, kg)	16.8±4.0	35.5±6.9	<0.001
Fat-free body mass (DEXA, kg)	48.3±9.0	55.6±11.3	<0.001
Abdominal VAT (MRI, cm^2)	82±39	212±98	<0.001
Abdominal SAT (MRI, cm^2)	151±43	332±88	<0.001
Cardiac parameters			
LV ejection fraction (%)	59.6±6.1	59.0±6.3	NS
LV end-diastolic volume (ml)	142±27	143±26	NS
LV stroke volume (ml)	84±17	84±15	NS
LV mass (g)	87±20	101±25	0.005
Indexed LV mass (g/m^2)	50±8	49±10	NS
LV mass/end-diastolic volume ratio	0.62±0.08	0.71±0.16	0.003
Heart rate (beats/min)	65±9	72±10	<0.001
Cardiac flow (l/min)	5.40±0.97	6.05±1.38	0.019
Vascular parameters			
Systolic blood pressure (mmHg)	115±11	124±15	0.004
Diastolic blood pressure (mmHg)	75±7	73±10	NS
Mean blood pressure (mmHg)	88±8	90±11	NS
Pulse pressure (mmHg)	40±6	51±11	<0.001
TAC (ml/mmHg)	2.11±0.46	1.71±0.42	<0.001
TPVR (mmHg/min per l)	16.8±3.0	15.5±3.4	0.034
Aortic PWV (m/s)	6.83±1.15	7.48±2.17	NS

DEXA, dual-energy X-ray absorptiometry; LV, left-ventricular; MRI, magnetic resonance imaging; NS, nonsignificant; PWV, pulse wave velocity; SAT, sub-cutaneous adipose tissue; TAC, total arterial compliance; TPVRs, total peripheral vascular resistances; VAT, visceral adipose tissue. All quantitative data are expressed as mean ± SD.

TABLE 2. Comparison of main recorded data between the control group and sub-groups of the abdominal obesity patients with (CR+) or without (CR−) LV concentric remodeling

		Abdominal obesity	
	Controls ($n=40$)	CR− ($n=50$)	CR+ ($n=20$)
Demographics			
Age (years)	54.8 ± 0.8	55.8 ± 0.7	55.7 ± 1.2
Men	21 (52%)	19 (38%)	17 (85%)†
Anthropometry			
Height (cm)	169 ± 1	167 ± 1	168 ± 2
Weight (kg)	64 ± 1	90 ± 1*	90 ± 2*
Body surface area (m^2)	1.73 ± 0.02	2.05 ± 0.02*	2.05 ± 0.03*
Body mass index (kg/m^2)	22.5 ± 0.4	32.3 ± 0.4*	31.6 ± 0.7*
$>30\,kg/m^2$	0 (0%)	35 (70%)*	13 (65%)*
Waist circumference (cm)	79 ± 1	105 ± 1*	105 ± 1*
Body composition			
Fat-body mass (DEXA, kg)	17.0 ± 0.9	35.9 ± 0.8*	34.8 ± 1.3*
Fat-free body mass (DEXA, kg)	47.9 ± 0.9	55.2 ± 0.8*	55.7 ± 1.3*
Abdominal VAT (MRI, cm^2)	81 ± 11	205 ± 10*	226 ± 17*
Abdominal SAT (MRI, cm^2)	151 ± 12	340 ± 11*	315 ± 17*
Cardiac parameters			
LV ejection fraction (%)	59.7 ± 0.9	58.8 ± 0.8	59.5 ± 1.4
LV end-diastolic volume (ml)	141 ± 4	149 ± 3	127 ± 5†
LV stroke volume (ml)	84 ± 2	87 ± 2	75 ± 4†
LV mass (g)	86 ± 2	95 ± 2*	114 ± 4*,†
Indexed LV mass (g/m^2)	49 ± 1	46 ± 1	55 ± 2*,†
LV mass/end-diastolic volume ratio	0.61 ± 0.01	0.64 ± 0.01	0.89 ± 0.02*,†
Heart rate (beats/min)	65 ± 1	71 ± 1*	76 ± 2*
Cardiac flow (l/min)	5.39 ± 0.20	6.17 ± 0.18*	5.73 ± 0.29
Vascular parameters			
Systolic blood pressure (mmHg)	115 ± 2	121 ± 2	131 ± 3*,†
Diastolic blood pressure (mmHg)	75 ± 1	71 ± 1	78 ± 2†
Mean blood pressure (mmHg)	88 ± 1	87 ± 1	96 ± 2*,†
Pulse pressure (mmHg)	40 ± 1	50 ± 1*	53 ± 2*
TAC (ml/mmHg)	2.10 ± 0.06	1.82 ± 0.06*	1.42 ± 0.09*,†
TPVR (mmHg/min per l)	16.8 ± 0.5	14.7 ± 0.5*	17.5 ± 0.7†
Aortic PWV (m/s)	6.84 ± 0.29	7.09 ± 0.26	8.46 ± 0.43*,†

All data are expressed as mean ± SEM and adjusted to sex, except for the variable 'men'. DEXA, dual-energy X-ray absorptiometry; LV, left-ventricular; MRI, magnetic resonance imaging; NS, nonsignificant; PWV, pulse wave velocity; SAT, sub-cutaneous adipose tissue; TAC, total arterial compliance; TPVRs, total peripheral vascular resistances; VAT, visceral adipose tissue.
*$P<0.05$ for comparisons with controls.
†$P<0.05$ for comparisons between CR+ vs. CR−.

obesity and control groups did not significantly differ in terms of age, sex ratio and height, but displayed marked differences in weight, BMI, body surface area and in body composition parameters (Table 1). General obesity ($>30\,kg/m^2$ BMI) was documented in 48 abdominal obesity patients (69%) and in none of the controls; and an untreated stage 1 hypertension (140–159 mmHg for systolic blood pressure and/or 90–99mmHg for diastolic blood pressure) was discovered at the preselection medical visit in 18 abdominal obesity patients (16%) and in none of the controls.

Left-ventricular mass was higher in abdominal obesity than in control patients (101 ± 25 vs. 87 ± 20 g, $P=0.005$) but this difference was no longer significant after indexation to body surface area (49 ± 10 vs. 50 ± 8 g/m^2). Only four abdominal obesity patients (20%) had a definite left-ventricular hypertrophy, as defined by a higher indexed left-ventricular mass than the sex-adjusted 95% confidence intervals (CIs) from controls.

The left-ventricular mass/end-diastolic volume ratio was higher in abdominal obesity than in the control group (0.71 ± 0.16 vs. 0.62 ± 0.08, $P=0.003$) and this ratio was higher than the sex-adjusted 95% CIs from controls (>0.78 for men and >0.74 for women) in 20 out of the 70 abdominal obesity patients (29%). These 20 patients, who included the four with left-ventricular hypertrophy, were considered to have a definite concentric remodeling (concentric remodeling+ group), whereas the remaining 50 abdominal obesity patients were not (concentric remodeling− group).

The abdominal obesity patients had a much higher pulse pressure than controls and thereby, their TAC index, determined by stroke volume-to-pulse pressure ratio, was markedly lower (in ml/mmHg: 1.71 ± 0.42 vs. 2.11 ± 0.46, $P<0.001$).

Abdominal obesity patients also had a higher cardiac flow than controls and their TPVR, as determined by the mean blood pressure-to-cardiac flow ratio, was lower (in mmHg/min per l: 15.5 ± 3.4 vs. 16.8 ± 3.0, $P=0.03$).

Characteristics of abdominal obesity patients with concentric remodeling (concentric remodeling+ group)

Compared to concentric remodeling−, concentric remodeling+ had a higher frequency of stage 1 hypertension (49 vs. 18%, $P=0.024$) and moreover, a high male predominance (85 vs. 38%, $P<0.001$). Thereby, the subsequent comparisons of quantitative variables between concentric

TABLE 3. Spearman correlation coefficients for significant correlates of LV mass/end-diastolic volume ratio

Demographics	
Age (years)	–
Obesity	+0.284
Women	−0.454
Anthropometry	
Height (cm)	+0.280
Weight (kg)	+0.377
Body surface area (m^2)	+0.408
BMI (kg/m^2)	+0.216
Waist circumference (cm)	+0.438
Body composition	
Fat body mass by DEXA (kg)	–
Fat-free body mass by DEXA (kg)	+0.483
Abdominal VAT at MRI (cm^2)	+0.451
Abdominal SAT at MRI (cm^2)	+0.394
Cardiac parameters	
LV ejection fraction (%)	–
LV end-diastolic volume (ml)	–
LV stroke volume (ml)	+0.403
Heart rate (beats/min)	+0.189
Cardiac flow (l/min)	–
Vascular parameters	
Systolic blood pressure (mmHg)	+0.249
Diastolic blood pressure (mmHg)	+0.227
Mean blood pressure (mmHg)	+0.242
Pulse pressure (mmHg)	–
TAC (ml/mmHg)	−0.200
TPVR (mmHg/min per l)	+0.438
Aortic PWV (m/s)	–

DEXA, dual-energy X-ray absorptiometry; LV, left-ventricular; MRI, magnetic resonance imaging; NS, nonsignificant; PWV, pulse wave velocity; SAT, sub-cutaneous adipose tissue; TAC, total arterial compliance; TPVRs, total peripheral vascular resistances; VAT, visceral adipose tissue.

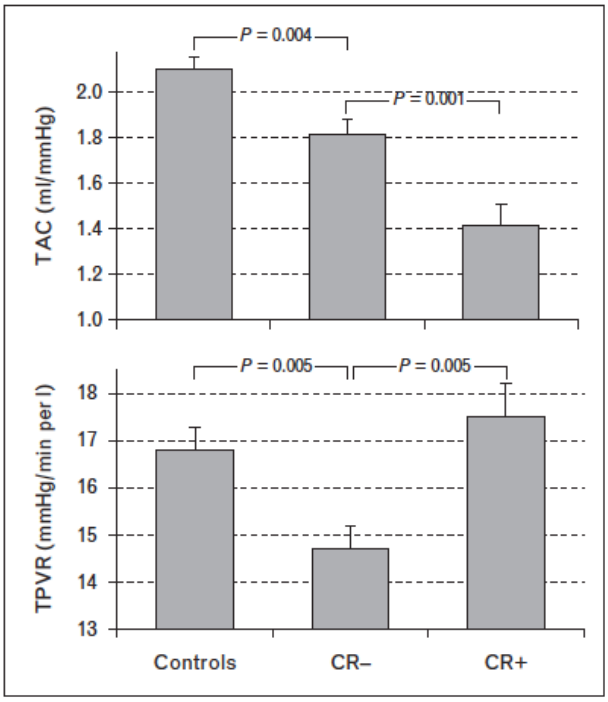


FIGURE 1 Comparison of the total arterial compliance index (TAC; upper panel) and of total peripheral resistances (TPVRs; lower panel) between controls ($n = 40$) and obese patients without (CR−; $n = 50$) or with (CR+; $n = 20$) left-ventricular concentric remodeling. Data are expressed as mean ± SEM after adjustment for sex differences. CR, concentric remodeling.

remodeling+, concentric remodeling− and controls were performed after sex adjustment (Table 2).

The high left-ventricular mass/end-diastolic volume ratio, which defined the concentric remodeling+ patients, was associated with higher absolute values of left-ventricular mass compared to both control and concentric remodeling− patients (Table 2). On average, the systolic and mean blood pressures of the concentric remodeling+ patients were mildly but significantly higher than in both concentric remodeling− and controls (Table 2).

Moreover, as detailed in Fig. 1, there was a step-by-step decline in TAC between controls (mean ± SEM: 2.10 ± 0.06 ml/mmHg), concentric remodeling− (1.82 ± 0.06 ml/mmHg) and concentric remodeling+ (1.42 ± 0.09 ml/mmHg, $P < 0.005$ for all inter-group comparisons). In addition, TPVRs were lower than controls for concentric remodeling− (14.7 ± 0.5 vs. 16.8 ± 0.5 ml/mmHg, $P = 0.005$) but not for concentric remodeling+ patients (17.5 ± 0.7 mmHg/min/ml). Aortic PWV was also higher in concentric remodeling+ than in both concentric remodeling− and controls (Table 2).

Correlates of the left-ventricular mass/end-diastolic volume ratio in the overall population

As detailed in Table 3, significant univariate correlates of the left-ventricular mass/end-diastolic volume ratio were: abdominal obesity and sex ratio; most anthropometric and body composition parameters; systolic, diastolic and mean blood pressures; and TAC and TPVR.

In multivariate analysis, the best independent correlates of the left-ventricular mass/end-diastolic volume ratio were: fat-free body mass ($P < 0.001$, positive correlation), TPVR ($P < 0.001$, positive correlation) and TAC ($P < 0.001$, negative correlation). This model predicted 51% of the variations in left-ventricular mass/end-diastolic volume (22% for fat-free body mass, 21% for TPVR and 8% for TAC). Importantly, the selected variables were unchanged when the analysis was restricted to only male patients or after having excluded patients with stage 1 hypertension.

DISCUSSION

The abdominal obesity patients represent a particular population with high rates of further developments of hypertension and of the metabolic syndrome and with definite increased risk of cardiovascular disease, especially at an advanced age [1–3]. In the present study, an early cardiovascular remodeling could be characterized in middle-aged patients, at a time when abdominal obesity is still uncomplicated or only marginally complicated by an untreated stage 1 hypertension (16% of our abdominal obesity patients). Indeed, as many as 29% of our abdominal obesity patients had evidence of a cardiac concentric remodeling at MRI, with higher left-ventricular mass/volume ratio, when compared to a normal reference population. Additionally, only 20% of these concentric remodeling patients had left-ventricular hypertrophy, strengthening the general consideration that concentric remodeling could be an early

sign of obesity-related cardiac remodeling, before the stage of definite left-ventricular hypertrophy [4–6,32].

The concentric remodeling patients frequently had an untreated stage 1 hypertension (45%) and moreover, they were predominantly men (85%), in accordance with the previous observations of low prevalence of left-ventricular remodeling in young and middle-aged women, before menopause [33,34]. In the final multivariate analysis, however, the selected independent correlates of the left-ventricular mass/end-diastolic volume ratio were not sex and/or blood pressure. They were fat-free body mass and two vascular parameters: TPVR and TAC index, giving evidence of a strong association between cardiac and vascular remodeling.

Concentric remodeling is considered as an initial adaptive response to increased left-ventricular afterload, such as in hypertension, with the addition of myocyte sarcomeres leading to increase in the left-ventricular wall thickness to a greater extent than left-ventricular cavity. However, left-ventricular afterload is not usually considered to be increased in uncomplicated obesity. On the contrary, TPVRs are generally decreased since the additional fat tissue constitutes a low-resistance circulatory compartment [13]. Accordingly, the mean TPVR of our abdominal obesity patients was slightly decreased compared with controls. In sub-group analyses, however, this decrease was still documented in only the abdominal obesity patients who had no concentric remodeling at MRI (Fig. 1). Hence, the level of TPVR of the concentric remodeling patients was inappropriately returned to the normal level of our control patients (i.e. in spite of the enhanced circulatory fat compartment), suggesting an early stage of the remodeling of peripheral vasculature. In support of this hypothesis, a remodeling of microvessels was already established in obese patients, with a decrease in vessel density and a stiffening of resistance arterioles [35,36]. Furthermore, obesity was recently shown to be associated with both hypertrophic remodeling and endothelial dysfunction of small resistance arteries and regardless of the presence of hypertension [37]. These changes were likely to decrease with weight reduction and in parallel to the evolution of blood markers of inflammation, but their exact mechanisms remain to be identified [37].

An additional mechanism of concentric remodeling might be the arterial stiffening, which is commonly documented in obese patients [4,14–17] and which is known to affect cardiac load, through deleterious changes in the characteristics of reflection waves, and play a role in the development of hypertension, left-ventricular hypertrophy and subsequent left-ventricular dysfunction [18,19]. Our concentric remodeling patients had an increased aortic PWV, an index of aortic stiffness [17], but this enhancement was limited (Table 2), in agreement with a recent MRI report in uncomplicated obesity [14]. In the present study, concentric remodeling was more strongly associated with the TAC index determined by the stroke volume/pulse pressure ratio (Fig. 1).

Total arterial compliance index is an expression of the compliance of the overall arterial tree [20,21,38] and hence provides a different information than aortic PWV. In previous studies of hypertensive patients, this TAC index was strongly linked to the echocardiographic pattern of concentric remodeling [20,21]. A similar relationship was observed herein, but with MRI and in abdominal obesity patients, strengthening the idea that arterial stiffening has a specific impact on the development of concentric remodeling [20].

Fat-free body mass was a last independent predictor of the concentric remodeling index, in addition to TAC and TPVR. Fat-free body mass was already shown to be linked to the left-ventricular mass of obese patients [31,39,40], presumably because certain metabolic, genetic and hormonal factors affect both fat-free body mass and left-ventricular mass [38,39]. In particular, adipocytokines, insulin and insulin-like growth factor, which are enhanced in obese patients, have direct trophic effects on the overall lean body mass including left-ventricular mass [32,41].

Limitations

One may wonder whether the male predominance of our concentric remodeling patients, as well as their higher rate of stage 1 hypertension, might have a confusing effect on our results. This is very unlikely since the univariate analyses performed for characterizing the concentric remodeling patients were adjusted to sex (Table 2) and results were not clearly modified by additional adjustments for systolic, mean or diastolic blood pressure (results not shown). Furthermore, results from the multivariate analysis were unchanged when restricted to only male patients or after having excluded patients with stage 1 hypertension.

Conversely, it must be recognized that this study is poorly informative on women, because of their very low rate of concentric remodeling. As already discussed above, this point could be better ascertained by further studies at a time frame more distant from menopause, when rates of left-ventricular remodeling are higher in women [33,34].

In addition, even if the resting blood pressure levels were not selected in the final multivariate analyses, pressure overload is likely to be involved in the mechanisms of the concentric remodeling of our abdominal obesity patients. The concentric remodeling patients had indeed changes in the compliance of great arteries and in the resistance of peripheral arteries, giving evidence of a remodeling from proximal to peripheral vasculature; and these changes are likely to affect cardiac load, not only through an increase in blood pressure level, but also through deleterious changes in reflection waves [20,21].

In conclusion, this MRI study shows that concentric remodeling is frequently documented in middle-aged patients with abdominal obesity, especially in men and in association with a decrease in TAC no longer counterbalanced by a decrease in TPVR, suggesting an extensive remodeling from proximal to peripheral vasculature. Whether the early reversal of these vascular changes by diet or drugs might lower concentric remodeling and cardiovascular risk, could be the subject of further MRI studies.

ACKNOWLEDGEMENTS

The authors wish to thank Mr Pierre Pothier for critical review of the manuscript.

Grant support: National Health Ministry (Programme Hospitalier de Recherche Clinique), French Institute of Health and Medical Research (INSERM), Lorraine Region

and the 6th framework program of the European Commission (Ingenious HyperCare Network of Excellence; contract number LSHM-CT-2006-037093).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006; 444:881–887.
2. de Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. *Eur Heart J* 2007; 28:850–856.
3. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, Eckel RH. American Heart Association; Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss. An update of the 1997 American Heart Association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. *Circulation* 2006; 113:898–918.
4. Rider OJ, Francis JM, Ali MK, Petersen SE, Robinson M, Robson MD, *et al*. Beneficial cardiovascular effects of bariatric surgical and dietary weight loss in obesity. *J Am Coll Cardiol* 2009; 54:718–726.
5. Rider OJ, Petersen SE, Francis JM, Ali MK, Hudsmith LE, Robinson MR, *et al*. Ventricular hypertrophy and cavity dilatation in relation to body mass index in females with uncomplicated obesity. *Heart* 2010; 97:203–208.
6. Turkbey EB, McClelland RL, Kronmal RA, Burke GL, Bild DE, Tracy RP, *et al*. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). *JACC Cardiovasc Imaging* 2010; 3:266–274.
7. Cheng S, Fernandes VR, Bluemke DA, McClelland RL, Kronmal RA, Lima JA. Age-related left ventricular remodeling and associated risk for cardiovascular outcomes: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2009; 2:191–198.
8. Bluemke DA, Kronmal RA, Lima JA, Liu K, Olson J, Burke GL, Folsom AR. The relationship of left ventricular mass and geometry to incident cardiovascular events: the MESA (Multi-Ethnic Study of Atherosclerosis) study. *J Am Coll Cardiol* 2008; 52:2148–2155.
9. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, *et al*. Adverse prognostic significance of concentric remodeling of the left ventricle in hypertensive patients with normal left ventricular mass. *J Am Coll Cardiol* 1995; 25:871–878.
10. Muiesan ML, Salvetti M, Monteduro C, Bonzi B, Paini A, Viola S, *et al*. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension* 2004; 43:731–738.
11. Lavie CJ, Milani RV, Ventura HO, Cardenas GA, Mehra MR, Messerli FH. Disparate effects of left ventricular geometry and obesity on mortality in patients with preserved left ventricular ejection fraction. *Am J Cardiol* 2007; 100:1460–1464.
12. Milani RV, Lavie CJ, Mehra MR, Ventura HO, Kurtz JD, Messerli FH. Left ventricular geometry and survival in patients with normal left ventricular ejection fraction. *Am J Cardiol* 2006; 97:959–963.
13. Ferrannini E. The haemodynamics of obesity: a theoretical analysis. *J Hypertens* 1992; 10:1417–1423.
14. Rider OJ, Tayal U, Francis JM, Ali MK, Robinson MR, Byrne JP, *et al*. The effect of obesity and weight loss on aortic pulse wave velocity as assessed by magnetic resonance imaging. *Obesity (Silver Spring)* 2010; 18:2311–2316.
15. Safar ME, Czernichow S, Blacher J. Obesity, arterial stiffness, and cardiovascular risk. *J Am Soc Nephrol* 2006; 17:S109–S1011.
16. Robinson MR, Scheuermann-Freestone M, Leeson P, Channon KM, Clarke K, Neubauer S, Wiesmann F. Uncomplicated obesity is associated with abnormal aortic function assessed by cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2008; 10:10.
17. Joly L, Perret-Guillaume C, Kearney-Schwartz A, Salvi P, Mandry D, Marie PY, *et al*. Pulse wave velocity assessment by external noninvasive devices and phase-contrast magnetic resonance imaging in the obese. *Hypertension* 2009; 54:421–426.
18. Nichols WW. Clinical measurement of arterial stiffness obtained from noninvasive pressure waveforms. *Am J Hypertens* 2005; 18:3S–10S.
19. Woodman RJ, Watts GF. Measurement and application of arterial stiffness in clinical research: focus on new methodologies and diabetes mellitus. *Med Sci Monit* 2003; 9:RA81–RA89.
20. Palmieri V, Bella JN, Roman MJ, Gerdts E, Papademetriou V, Wachtell K, *et al*. Pulse pressure/stroke index and left ventricular geometry and function: the LIFE Study. *J Hypertens* 2003; 21:781–787.
21. Palmieri V, Bella JN, Gerdts E, Wachtell K, Papademetriou V, Nieminen MS, *et al*. Change in pulse pressure/stroke index in response to sustained blood pressure reduction and its impact on left ventricular mass and geometry changes: the life study. *Am J Hypertens* 2008; 21:701–707.
22. Alberti KGMM, Zimmet P, Shaw J. Metabolic syndrome-a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetic Med* 2006; 23:469–480.
23. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2008; 31:S55–S60.
24. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, *et al*. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; 42:1206–1252.
25. Quilliot D, Alla F, Böhme P, Bruntz JF, Hammadi M, Dousset B, *et al*. Myocardial collagen turnover in normotensive obese patients: relation to insulin resistance. *Int J Obes (Lond)* 2005; 29:1321–1328.
26. Codreanu A, Djaballah W, Angioi M, Ethevenot G, Moulin F, Felblinger J, *et al*. Detection of myocarditis by contrast-enhanced MRI in patients presenting with acute coronary syndrome but no coronary stenosis. *J Magn Reson Imaging* 2007; 25:957–964.
27. Mandry D, Lapicque F, Odille F, Djaballah W, Codreanu A, Escanyé JM, *et al*. Multicompartmental analysis of late contrast enhancement in areas of myocardial infarction supplied by chronically occluded coronary arteries. *J Magn Reson Imaging* 2009; 29:78–85.
28. Shen W, Punyanitya M, Chen J, Gallagher D, Albu J, Pi-Sunyer X, *et al*. Visceral adipose tissue: relationships between single slice areas at different locations and obesity-related health risks. *Int J Obes (Lond)* 2007; 31:763–769.
29. Demerath EW, Shen W, Lee M, Choh AC, Czerwinski SA, Siervogel RM, Towne B. Approximation of total visceral adipose tissue with a single magnetic resonance image. *Am J Clin Nutr* 2007; 85:362–368.
30. Lee S, Janssen I, Ross R. Interindividual variation in abdominal subcutaneous and visceral adipose tissue: influence of measurement site. *J Appl Physiol* 2004; 97:948–954.
31. Armao D, Guyon JP, Firat Z, Brown MA, Semelka RC. Accurate quantification of visceral adipose tissue (VAT) using water-saturation MRI and computer segmentation: preliminary results. *J Magn Reson Imaging* 2006; 23:736–741.
32. Litwin SE. Cardiac remodeling in obesity: time for a new paradigm. *JACC Cardiovasc Imaging* 2010; 3:275–277.
33. Agabiti-Rosei E, Muiesan ML. Left ventricular hypertrophy and heart failure in women. *J Hypertens Suppl* 2002; 20:S34–S38.
34. Schillaci G, Verdecchia P, Borgioni C, Ciucci A, Porcellati C. Early cardiac changes after menopause. *Hypertension* 1998; 32:764–769.
35. Stapleton PA, James ME, Goodwill AG, Frisbee JC. Obesity and vascular dysfunction. *Pathophysiology* 2008; 15:79–89.
36. Jonk AM, Houben AJ, de Jongh RT, Serné EH, Schaper NC, Stehouwer CD. Microvascular dysfunction in obesity: a potential mechanism in the pathogenesis of obesity-associated insulin resistance and hypertension. *Physiology (Bethesda)* 2007; 22:252–260.
37. De Ciuceis C, Porteri E, Rizzoni D, Corbellini C, La Boria E, Boari GE, *et al*. Effects of weight loss on structural and functional alterations of subcutaneous small arteries in obese patients. *Hypertension* 2011; 58:29–36.
38. Chemla D, Hebert JL, Coirault C, Zamani K, Suard I, Colin P, Lecarpentier Y. Total arterial compliance estimated by stroke volume-to-aortic pulse pressure ratio in humans. *Am J Physiol* 1998; 274:H500–H505.
39. Bella JN, Devereux RB, Roman MJ, Palmieri V, Liu JE, Paranicas M, *et al*. Relations of left ventricular mass to fat-free and adipose body mass: the strong heart study. The Strong Heart Study Investigators. *Circulation* 1998; 98:2538–2544.
40. Rider OJ, Francis JM, Ali MK, Byrne J, Clarke K, Neubauer S, Petersen SE. Determinants of left ventricular mass in obesity; a cardiovascular magnetic resonance study. *J Cardiovasc Magn Reson* 2009; 11:9.
41. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol Rev* 2008; 88:389–419.

4.2 Identification de marqueurs pronostiques au stade B: Post-infarctus du myocarde

La cardiopathie ischémique représente la très grande majorité des causes d'IC du fait d'un remodelage ventriculaire gauche délétère à moyen et long termes. En effet ce remodelage est dorénavant l'élément clé du suivi des patients aux antécédents de cardiopathie ischémique car la mortalité précoce intra-hospitalière est en très nette régression.

Malheureusement les éléments cliniques actuels sont imparfaits pour prédire les patients les plus à risque de développer un remodelage délétère. Le dépôt de fibrose myocardique a été identifié comme un des éléments clés de ce remodelage.

L'objectif de ce travail était d'évaluer l'intérêt de l'ajout des peptides collagéniques à des paramètres classiques afin d'améliorer la prédiction de la survenue de remodelage. Notre population est constituée de 206 patients ayant présenté un syndrome coronarien aigu antérieur avec sus décalage du segment ST.

Nous avons pu mettre en évidence que les peptides collagéniques et plus particulièrement le ratio PIIINP/ICTP, était positivement et indépendamment associé au développement d'un remodelage ventriculaire gauche à 1 an ainsi qu'aux décès cardiovasculaires et aux hospitalisations pour IC à 3 ans. De plus ce ratio permet d'identifier des patients à haut risque de remodelage non « repérés » par des critères classiques et validés tels que la fraction d'éjection du ventricule gauche à la sortie d'hospitalisation et le Brain Natriuretic Peptide (BNP).

4.2.1 *Extracellular matrix turnover biomarkers predict long term left ventricular remodeling after myocardial infarction (insights from the REVE-2 study).*

Romain Eschalier M.D., Marie Fertin M.D.,Ph.D., Renaud Fay PharmD., Christophe Bauters M.D., Faïez Zannad M.D.,Ph.D., Florence Pinet Ph.D. and Patrick Rossignol M.D.,Ph.D..

Ce manuscript est accepté pour publication dans “Circulation: Heart Failure”.

Title: Extracellular matrix turnover biomarkers predict long term left ventricular remodeling after myocardial infarction (insights from the REVE-2 study).

Manuscript number: CIRCHF/2013/000403R1

Author(s): Patrick Rossignol, CHU Nancy & Université de Lorraine & INSERM
Romain Eschalier, Clermont University Hospital
Marie Fertin, CHU Lille, Lille, F-59000 France
Renaud Fay, INSERM, Centre d'Investigation Clinique CIC-P 9501, Nancy, F-54000 France
C. Bauters, Hopital de Lille
Faiez Zannad, Inserm, Université de Lorraine and CHU, Nancy, France
Florence Pinet, INSERM U744

Extracellular matrix turnover biomarkers predict long term left ventricular remodeling after myocardial infarction (insights from the REVE-2 study).

Eschalier *et al.*

Short Title: Cardiac fibrosis after myocardial infarction

Romain Eschalier M.D., Marie Fertin M.D.,Ph.D., Renaud Fay PharmD., Christophe Bauters M.D., Faïez Zannad M.D.,Ph.D., Florence Pinet† Ph.D. and Patrick Rossignol*† M.D.,Ph.D..

From the INSERM, Centre d'Investigation Clinique CIC-P 9501, Nancy, F-54000 France (RE, RF, FZ, PR) ; CHU Nancy, Department of Cardiology, Nancy, F-54000 France (FZ) ; Université de Lorraine, Nancy, F-54000 France (FZ, PR) ; INSERM, U1116, Nancy, F-54000 France (FZ, PR) ; Clermont Université, Université d'Auvergne, UMR6284, F-63000 Clermont-Ferrand France (RE) ; CHU Clermont-Ferrand, Department of Cardiology, F-63000 Clermont-Ferrand France (RE); CHU Lille, Lille, F-59000 France (MF, CB, FP) ; Inserm U744, Institut Pasteur de Lille, Université de Lille 2, Lille, F-59000 France (MF, CB, FP) ; Faculté de Médecine de Lille, Lille, F-59000 France (CB).

* Corresponding author: Patrick Rossignol, CIC Plurithématique. Institut Lorrain du cœur et des vaisseaux. 4 rue du Morvan. 54500 Vandœuvre lès Nancy – France. Tel: +33.3.83.15.73.22; Fax: +33.3.83.15.73.24; e-mail: p.rossignol@chu-nancy.fr

† Both last co-authors.

Total word count: 5640

Journal Subject Codes: 4; 16; 108; 115;

ABSTRACT

Background. Extracellular matrix turnover plays a key role in wound repair post-myocardial infarction (MI). The aim of the study was to evaluate whether biomarkers of myocardial fibrosis measurements one month after MI may predict left ventricular (LV) remodeling.

Methods and Results. This prospective multicenter study included 246 patients with a first anterior Q-wave MI. Echocardiographic studies were performed at hospital discharge and 12 months after MI. Brain natriuretic peptide (BNP) as well as biomarkers of myocardial fibrosis (ICTP: type 1 collagen telopeptide; PINP: aminoterminal propeptide of type I procollagen; PIIINP: aminoterminal propeptide of type III procollagen) were measured one month after MI in 218 patients.

In multivariate analysis, PIIINP/ICTP ratio ≤1 [OR (95%CI): 1.86(1.02-3.39), p=0.043] one month after MI, and BNP >100pg/ml [OR: 2.35(1.28-4.31, p=0.006] were associated with a pejorative LV remodeling whereas LV ejection fraction at discharge [per 5% increment: OR: 0.78(0.65-0.94), p=0.01] was independently associated with lower rates of detrimental LV remodeling at 12 months. Patients with high BNP and PIIINP/ICTP ratio ≤1, measured one month after MI, had the highest risk of developing a primary composite event (cardiovascular death or hospitalization for worsening heart failure: 14 events/216 patients, p=0.0001) during a 3-year follow-up.

Conclusions. Myocardial fibrosis turnover after MI is associated with LV remodeling. Low PIIINP/ICTP ratio (≤1) at one month is predictive, in addition to BNP and LV ejection fraction, of detrimental LV remodeling as well as cardiovascular deaths and hospitalizations for heart failure.

KEYWORDS

Myocardial infarction; cardiac remodeling; myocardial fibrosis; PIIINP; ICTP.

INTRODUCTION

Despite a recent decrease [1], the incidence of acute myocardial infarction (MI) remains elevated [2] and is associated with a substantial mortality within 6 months [3]. The long-term prognosis of myocardial infarction is dependent on left ventricular (LV) remodeling (evaluated by LV dilatation) which is a well-documented surrogate indicating a high risk for heart failure onset and cardiovascular death [4]. Although several risk factors have been identified (e.g. anterior infarct location, infarct size, LV ejection fraction at discharge) [5], the ability to predict LV remodeling remains difficult. Several studies have attempted to reduce LV remodeling by acting on different pathways, mostly aimed at decreasing LV overload, myocardial fibrosis or inflammation during the acute phase of myocardial infarction [6–8]. We previously reported that cardiac extracellular matrix turnover (assessed by circulating collagen peptides) is associated with clinical outcome in patients with heart failure and reduced ejection fraction (HFREF) post MI, independently from cardiac congestion [assessed by brain natriuretic peptide (BNP)], and may be targeted by mineralocorticoid receptor antagonists [6]. Moreover, extracellular matrix turnover days and weeks after MI have been shown to contribute to the decline in cardiac function and eventual failure [9–12]. We also reported that a dual determination of BNP and cardiac troponin I (cTnI) one month after MI (but importantly not at baseline) may help refine the prediction of LV remodeling: indeed, BNP is increased in response to LV overload while an increase in cTnI may indicate myocyte injury. In contrast CRP, a marker of inflammation, was found not to be associated with LV remodeling [13]. The aim of the present study was to assess whether myocardial fibrosis, evaluated by collagen peptide measurements one month after myocardial infarction, could have additional predictive value of LV remodeling post Q-wave anterior MI.

METHODS

Study population

The design as well as inclusion and exclusion criteria of the REVE-2 study have been published in detail elsewhere [13]. The study consisted in a prospective multicenter study designed to analyze the association of circulating biomarkers with LV remodeling in patients with a first anterior wall Q-wave MI [14]. Patients were enrolled from February 2006 to September 2008. Inclusion criteria were hospitalization within 24 h after symptom onset and a pre-discharge echocardiogram showing at least 3 akinetic LV segments in the infarct zone. Exclusion criteria were inadequate quality of the echocardiographic image, life-limiting noncardiac disease, significant valvular disease or a prior Q-wave MI. The institutional Ethics Committee (Centre Hospitalier Universitaire de Lille) approved the study, and written informed consent was obtained from all patients. No clinical trials.gov number was assigned to this study since it started in 2006.

Clinical follow-up

Clinical follow-up was performed at outpatient visits or by contacting the general practitioner or cardiologist between February 2009 and June 2011. Collected data included hospitalization for heart failure (symptoms of dyspnea or edema associated with bilateral rales, elevated venous pressure, or interstitial or alveolar edema on chest X-ray, or the addition of intravenous diuretics or inotropic medications) and death.

Echocardiographic assessment

Serial echocardiographic studies were performed at hospital discharge (day 3 to 7), 3 months and 12 months after initial MI. A standard echocardiographic imaging protocol was used, with apical 4- and 2-chamber views; 2D echocardiograms of the LV short axis were recorded from the left parasternal region at 3 levels: the mitral valve, the mid papillary muscle and apex. All echocardiograms were analyzed at the Lille Core Echo Laboratory (Lille, France), as previously described [15]. LV end-diastolic volume (EDV), end-systolic volume (ESV) and ejection fraction (EF) were calculated with a modified monoplane Simpson's rule. LV remodeling was defined as a greater than 20% increase in LVEDV 12 months after initial MI [15,16].

Biological parameters assessment

Biomarkers were measured in plasma and serum samples obtained at 1 month after MI. Plasma and serum were collected in glass tubes and processed within 2 hours. Samples were stored at -80°C. Samples underwent no more than 2 freeze/thaw cycles before analysis in a core laboratory (Lille, France for BNP and Nancy, France for collagen peptides).

Brain natriuretic peptide was measured with a fully automated 2-site sandwich immunoassay on an Advia Centaur analyzer (Siemens Diagnostic, Zurich, Switzerland). The lowest measurable concentration with this assay with a ≤ 20% coefficient of variation is 2.5 pg/mL. The accuracy of this technique is 2.3–4.7%.

Radioimmunoassay kits (Orion Diagnostica, Espoo, Finland) were used for determination of serum collagen peptide concentrations [PINP: aminoterminal propeptide of type I procollagen (reference range: 22 to 87 and 19 to 83 ng/mL in men and women, respectively); PIIINP: aminoterminal propeptide of type III procollagen, biomarkers of collagen synthesis (reference range: 2.3 to 6.4 ng/mL); ICTP: type 1 collagen telopeptide, biomarker of collagen degradation (reference range: 3.2 to 3.5 ng/mL)] as previously reported [6,17] with interassay variations < 9.8%.

Cardiac troponin I was measured in plasma samples using a 3-site sandwich immunoassay on an Advia Centaur. The lowest concentration measurable with this assay with a ≤ 20% coefficient of variation is 0.015 ng/ml. Cardiac troponin I in the 99th percentile in healthy subjects is 0.05 ng/ml, with 10% coefficient of variation for this threshold. The accuracy of this technique is 2.7% to 5.3%.

C-reactive protein was measured in serum samples using a sensitive latex-enhanced immunonephelometric method with the automated BNII nephelometer (Siemens Diagnostic). The minimum sensitivity for this assay is 0.15 mg/L.

Estimated glomerular filtration rate (eGFR) was computed using the 4-variable MDRD (Modification of Diet in Renal Disease) Study formula [18].

Statistical analysis

All analyses were carried out using the SAS 9.2 software (SAS Institute, Cary, NC, USA). The two-tailed significance level was set at $p < 0.05$. Factors associated with LV remodeling, defined as an increase > 20% of LV end-diastolic volume 12 months after MI, were first identified using univariate (after logarithmic transformation for

collagen biomarkers) then by multivariate logistic regression. Significant covariables were identified among all patient characteristics listed in Table 1, i.e. baseline characteristics and 1-month biomarker levels. Multivariate models retained only significant covariables. Validity assumptions of the multivariate models were thoroughly verified: BNP and PIIINP/ICTP ratio were dichotomized in order to meet the log-linearity condition. The cut-off values (> *vs.* ≤ 100 ng/l for BNP and ≤ *vs.* >1 for PIIINP/ICTP ratio, roughly corresponding to the medians) were selected from receiver operating characteristic (ROC) analysis as the best balance between sensitivity and specificity according to the Youden and the 'closest to (0,1)' criteria [19]. Results of logistic regressions were presented as odds ratios and their 95% confidence intervals [OR (95%CI)]. Event-free survival was illustrated using Kaplan-Meyer curves for clinical outcome. Following these analyses, patient characteristics were presented according to PIIINP/ICTP ratio as means ± standard deviation or percentages as appropriate. Between-group comparisons were performed using the Mann-Whitney and Chi-Square tests when appropriate.

RESULTS

Patient characteristics (Table 1)

A total of 246 patients were included in the REVE-2 study. One-year echocardiographic follow-up was achieved in 226 patients. Collagen peptide measurements were achieved in 218 patients. Therefore, our study population included 206 patients with both collagen peptide measurements 1 month after initial myocardial infarction and one-year echocardiographic follow-up. The characteristics of these 206 patients are summarized in Table 1.

Left ventricular remodeling (> 20% increase in LV end-diastolic volume 12 months after myocardial infarction) was observed in 87/218 patients (40%). The median time of follow-up was 36 months, during which 14/216 patients presented clinical outcome (8 with hospitalization as only event, 4 with death as second event, 2 with death as first event).

Association of extracellular matrix remodeling biomarkers at 1 month and LV remodeling

In univariate analysis the PIIINP/ICTP ratio [2.09 (1.11 - 3.95) per decreasing $\log_e$, p = 0.023] measured 1 month post MI, BNP measured at 1 month [1.72 (1.24 - 2.37) per $\log_e$, p = 0.001] and cTnI ≥ 0.05µg/l at 1 month [2.19 (1.08 - 4.44), p = 0.030] were associated with a pejorative LV remodeling, whereas higher LV ejection fraction at discharge [OR (95%CI): 0.75 (0.62 - 0.89) per 5% increment, p = 0.001] was independently associated with lower rates of detrimental LV remodeling 12 months after initial Q-wave anterior MI. (Table 2)

Similarly, in multivariate analysis, PIIINP/ICTP ratio ≤1 one month after MI [OR : 1.86 (1.02 – 3.39), p = 0.043] and BNP > 100pg/ml at 1 month [OR : 2.35 (1.28 - 4.31), p = 0.006] were associated with a pejorative LV remodeling, whereas higher LV ejection fraction at discharge [(per 5% increment): OR : 0.78 (0.65 - 0.94), p = 0.010] was independently associated with lower rates of detrimental LV remodeling 12 months after initial Q-wave anterior MI. The discriminant power of the model (Harrell's c statistic) was 0.698.

Accordingly, patients with reduced ejection fraction (LV ejection fraction < 50%, cutoff value determined using ROC analysis) and/or BNP > 100 pg/ml were more likely to develop LV remodeling 12 months after initial MI. Interestingly PIIINP/ICTP ratio ≤ 1 one month after initial myocardial infarction was able to identify twice (17% to 40%) more patients with BNP ≤ 100ng/l, and twice (21% to 42%) more patients with LV ejection fraction > 50% in whom LV remodeling ultimately developed at 12 months (Figures 1 and 2). Adding PIIINP/ICTP ratio (≤1) to LVEF and BNP (≤ 100ng/l) improved the sensitivity and the specificity of the model by 1.4% and 0.5% respectively, for an integrated discrimination improvement (IDI) of 1.9% (p = 0.051).

Association of extracellular matrix remodeling biomarkers at 1 month and clinical outcome

Ten of the 14 clinical outcomes (70%) were observed in patients with BNP > 100ng/l and PIIINP/ICTP ratio ≤ 1 at 1 month. The additional predictive value of the combination of BNP and PIIINP/ICTP levels for the risk of composite outcome are presented in Figure 3.

Baseline features of patients according to their PIIINP/ICTP ratio at one month.

Clinical characteristics of patients with PIIINP/ICTP ratio ≤ and > 1 at 1 month (table 1) were very similar, except for DBP (61 ± 12 *vs.* 64 ± 10 mmHg, p = 0.036) and eGFR (81 ± 25 *vs.* 88 ± 20 ml/min/1.73m², p = 0.026). Patients with a PIIINP/ICTP ratio ≤ 1 had higher BNP [99 (56 – 219) *vs.* 79 (44 – 145) ng/l, p = 0.036), proportion of patients with cTnI ≥0.05µg/l [24 (25%) *vs.* 12 (13%), p = 0.034] and myocardial fibrosis turnover favoring degradation [(PIIINP: 4.03 (3.45 - 4.98) *vs.* 6.28 (5.23 - 7.70) µg/l, p < 0.0001) and (ICTP: 5.29 (4.51 - 7.11) *vs.* 4.45 (3.69 - 5.16) µg/l, p < 0.0001)].

DISCUSSION

The results of the present study confirm that myocardial fibrosis turnover (as assessed herein by the PIIINP/ICTP ratio) is critical after a first anterior wall myocardial infarction and probably plays a key role in LV remodeling despite optimal management (initial reperfusion therapy and use of optimal medical treatment at hospital discharge). Left ventricular remodeling was observed in 40% of our study patients despite this optimal management. Myocardial fibrosis turnover measured one month after myocardial infarction was associated with LV remodeling at 12 months independently from other classical pathways such as pressure overload (BNP), inflammation (CRP) or initial myocardial injury (LV ejection fraction and cTnI). Of note, cTnI measurements one month after initial MI were significantly associated with LV remodeling at 12 months (p = 0.03) [13], but were no longer significant in multivariate models including BNP at 1 month, LVEF at discharge and PIIINP/ICTP

ratio at 1 month. This may suggest that, after an initial myocardial injury, extracellular matrix turnover and LV pressure overload could be the main factors leading to LV remodeling at 12 months after an anterior MI. Furthermore, in addition to LV ejection fraction at discharge and BNP measurements at month 1, PIIINP/ICTP ratio measured one month after MI may help to improve risk prediction of LV remodeling at 12 months and of a primary event at 3 years (cardiovascular death or hospitalization for worsening heart failure) after a first anterior wall MI.

In the post-myocardial infarction heart, there is a time-dependent damage to myocytes and the extracellular matrix (ECM) in the infarct zone, followed by gradual reparation with fibrosis. The non-infarct zone exhibits reactive hypertrophy, interstitial fibrosis and increased collagen, leading to cardiac dysfunction and progressive dilation. Therefore, in such pathological conditions, ECM remodeling may lead to myocardial fibrosis in addition to having deleterious effects on pumping capacity and diastolic function [17].

In the present study, it was decided to measure myocardial fibrosis biomarkers one month after initial myocardial infarction since we previously reported that, at this particular time, high BNP levels in REVE 2 patients were associated with adverse remodeling and that the highest levels of extracellular matrix turnover biomarkers were similarly observed at this time after MI in the EPHESUS study, but in which echo data were unfortunately not available [6]. In this latter study patients were enrolled post-MI HFREF (mean LVEF: 33 ± 6%) and mostly with HF symptoms (90% of the overall population) while HF symptoms were only present in 31% in REVE-2 study (30% with LVEF ≤ 45%). The combination of baseline BNP and ICTP values above the median was associated with a higher risk of CV death or HF

hospitalization [HR = 3.03 (1.49 - 6.16), p = 0.002] in EPHESUS [6].

We also decided to perform PIIINP measurements (a biomarker of collagen synthesis) since it appears to be the main component of "reactive" ischemic-related fibrosis, and can be synthesized in a more rapid and reactive manner in addition to playing an important role in the development of new areas of myocardial fibrosis [20]. Concomitantly, a higher ICTP level (a biomarker of collagen degradation) indicates an intensive and deleterious extracellular matrix turnover leading to LV remodeling and was previously found as a predictor of LV remodeling after myocardial infarction [21,22], as it tended to be in the present study, in the univariate analysis of the left ventricular remodeling – associated factors (Table 2). Furthermore, we previously reported that serum ICTP was associated with all-cause death [6,23] and chronic HF symptoms onset [23] in post-myocardial infarction. Thus, extracellular matrix turnover by PIIINP/ICTP ratio was ultimately assessed, including biomarkers of collagen synthesis (PIIINP) and degradation (ICTP) measured one month after MI.

To our knowledge, this is the first report in which ECM turnover was found associated with LV remodeling one year post MI, independently from other classical pathways such as inflammation, pressure overload or initial myocardial injury. Furthermore, in association with BNP, PIIINP/ICTP ratio (≤1) was able to predict the risk at 3 years of cardiovascular death or hospitalization for worsening heart failure in post-myocardial infarction patients.

Importantly, we were also able to show such association in patients who mostly presented with non complicated myocardial infarction (70% of patients with Killip class <2, mean CPK peak ~3000UI/l, mean LV ejection fraction ~50% and only 30% of patients with LVEF ≤ 45%) in comparison with other studies which highlighted this association in patients presenting with a myocardial infarction and a low LV ejection

fraction and/or heart failure symptoms [6,24].

Several studies have attempted to develop risk scores in order to predict cardiovascular outcomes and LV remodeling in patients with myocardial infarction [2,3,5]. Such scores were solely based on the patients' clinical and biological characteristics, and type of myocardial infarction. Unfortunately, these scores were not completely effective in suitably predicting and identifying patients at high risk of developing cardiac remodeling after myocardial infarction, hence the reason for choosing to measure PIIINP/ICTP ratio, in addition to BNP and LV ejection fraction, in the present study. Interestingly, low PIIINP/ICTP ratio (≤ 1) could help to predict LV remodeling at 12 months more specifically in known low-risk patients (BNP ≤100 ng/l and LVEF > 50%) than in high-risk patients (BNP > 100 ng/l and LVEF ≤ 50%) (Figures 1 and 2).

This risk prediction based on PIIINP/ICTP ratio assessed at 1 month in addition to LV ejection fraction at discharge or BNP at 1 month may help clinicians to identify patients at high risk of developing LV remodeling. Patients with low PIIINP/ICTP ratio (≤1) and high BNP one month after myocardial infarction may thus be treated more "aggressively" with an optimization of the doses of the different drugs used. Indeed, we previously reported that mineralocorticoid receptor antagonists (MRAs) decrease ECM turnover and thus may decrease LV remodeling [6]. Moreover, several studies (i.e. Albatross and Reminder trials) are currently ongoing or recent to confirm the benefit of MRAs in preventing LV remodeling in all cases of myocardial infarction [7]. In the present study, no significant difference in terms of medical treatment at discharge with regard to PIIINP/ICTP levels was observed, although the observational design of REVE 2 precludes from inferring any causal relationship. Importantly, because of its stability PIIINP/ICTP ratio could be a good alternative to detect patients prone to

develop LV remodeling after an initial Q-wave anterior myocardial infarction compared to BNP and LVEF.

STUDY LIMITATIONS

Echocardiography was used herein to assess LV remodeling. Currently, cardiac magnetic resonance imaging has been associated with lower variability and appears as the best technique for LV remodeling assessment [25]. Echocardiography, however, due to its greater availability and to technological advances, is also an appropriate option, especially when multicenter recruitment is considered. Due to the low number of events of composite clinical outcome (14/216; cardiovascular deaths or hospitalizations for worsening heart failure), we acknowledge a lack of robustness of life table result (Figure 3). Furthermore, our study population is to date the largest published pre-specified biomarkers analysis survey to evaluate LV remodeling in post-myocardial infarction. Finally, our interpretation of PIIINP concentrations is based on the current assumption shared by most authors that it depicts collagen type III synthesis, whereas earlier studies from Jensen's group proposed that serum PIIINP may originate from ongoing synthesis or degradation of type III collagen fibrils with PIIINP on their surface [26].

CONCLUSIONS

The ability to predict LV remodeling is difficult. Myocardial fibrosis turnover after MI is associated with LV remodeling. In the present study, low PIIINP/ICTP ratio (≤1), at

one month, is predictive of detrimental LV remodeling at 12 months after Q-wave anterior myocardial infarction and may also predict, along with BNP and LV ejection fraction, cardiovascular deaths and hospitalizations for worsening heart failure at 3 years. Further studies are needed to evaluate early interventions on myocardial fibrosis turnover after MI to prevent LV remodeling.

ACKNOWLEDGMENTS

The investigators thank Stéphane Dequand and Michel Deneve for monitoring the study and for their help in the Lille Core Echocardiographic Laboratory. We thank Ms Leroy (Nancy CIC) for her skillful technical assistance. We thank Mr. Pierre Pothier for the editing of this manuscript.

FUNDING SOURCES

The studies were supported by the CHRU de Lille PHRC 2005R/1901; the Fondation de France, Paris; ANR (ANR-11-EMMA-029-01) (main study) and the Lorraine region (collagen peptide measurements) and E.U. FP7 HOMAGE (305507) projects; The «Fédération Française de Cardiologie».

DISCLOSURES

None.

REFERENCES

1. Puymirat E, Simon T, Steg PG, Schiele F, Guéret P, Blanchard D, Khalife K, Goldstein P, Cattan S, Vaur L, Cambou J-P, Ferrières J, Danchin N. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA*. 2012; 308:998–1006.

2. Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D, ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document Reviewers, Hasdai D, Astin F, Astrom-Olsson K, Budaj A, Clemmensen P, Collet J-P, Fox KA, Fuat A, Gustiene O, Hamm CW, Kala P, Lancellotti P, Maggioni AP, Merkely B, Neumann F-J, Piepoli MF, Van de Werf F, Verheugt F, Wallentin L. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *European Heart Journal*. 2012; 33:2569–2619.

3. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation

with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006; 333:1091.

4. St John Sutton M, Pfeffer MA, Plappert T, Rouleau JL, Moyé LA, Dagenais GR, Lamas GA, Klein M, Sussex B, Goldman S. Quantitative two-dimensional echocardiographic measurements are major predictors of adverse cardiovascular events after acute myocardial infarction. The protective effects of captopril. *Circulation*. 1994; 89:68–75.

5. Gaudron P, Eilles C, Kugler I, Ertl G. Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors. *Circulation*. 1993; 87:755–763.

6. Iraqi W, Rossignol P, Angioi M, Fay R, Nuée J, Ketelslegers JM, Vincent J, Pitt B, Zannad F. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. *Circulation*. 2009; 119:2471–2479.

7. Beygui F, Vicaut E, Ecollan P, Machecourt J, Van Belle E, Zannad F, Montalescot G. Rationale for an early aldosterone blockade in acute myocardial infarction and design of the ALBATROSS trial. *Am. Heart J.* 2010; 160:642–648.

8. Mewton N, Croisille P, Gahide G, Rioufol G, Bonnefoy E, Sanchez I, Cung TT, Sportouch C, Angoulvant D, Finet G, André-Fouët X, Derumeaux G, Piot C, Vernhet H, Revel D, Ovize M. Effect of cyclosporine on left ventricular remodeling after reperfused myocardial infarction. *J. Am. Coll. Cardiol.* 2010;

55:1200–1205.

9. Sun Y, Weber KT. Infarct scar: a dynamic tissue. *Cardiovasc. Res.* 2000; 46:250–256.

10. Lindsey ML, Mann DL, Entman ML, Spinale FG. Extracellular matrix remodeling following myocardial injury. *Ann. Med.* 2003; 35:316–326.

11. Bowers SLK, Banerjee I, Baudino TA. The extracellular matrix: at the center of it all. *J. Mol. Cell. Cardiol.* 2010; 48:474–482.

12. Jourdan-Lesaux C, Zhang J, Lindsey ML. Extracellular matrix roles during cardiac repair. *Life Sci.* 2010; 87:391–400.

13. Fertin M, Hennache B, Hamon M, Ennezat PV, Biausque F, Elkohen M, Nugue O, Tricot O, Lamblin N, Pinet F, Bauters C. Usefulness of serial assessment of B-type natriuretic peptide, troponin I, and C-reactive protein to predict left ventricular remodeling after acute myocardial infarction (from the REVE-2 study). *Am. J. Cardiol.* 2010; 106:1410–1416.

14. Fertin M, Beseme O, Duban S, Amouyel P, Bauters C, Pinet F. Deep plasma proteomic analysis of patients with left ventricular remodeling after a first myocardial infarction. *Proteomics Clin Appl*. 2010; 4:654–673.

15. Savoye C, Equine O, Tricot O, Nugue O, Segrestin B, Sautière K, Elkohen M, Pretorian EM, Taghipour K, Philias A, Aumégeat V, Decoulx E, Ennezat PV, Bauters C. Left ventricular remodeling after anterior wall acute myocardial infarction in modern clinical practice (from the REmodelage VEntriculaire [REVE] study group). *Am. J. Cardiol.* 2006; 98:1144–1149.

16. Temporelli PL, Giannuzzi P, Nicolosi GL, Latini R, Franzosi MG, Gentile F, Tavazzi L, Maggioni AP. Doppler-derived mitral deceleration time as a strong prognostic marker of left ventricular remodeling and survival after acute myocardial infarction: results of the GISSI-3 echo substudy. *J. Am. Coll. Cardiol.* 2004; 43:1646–1653.

17. Zannad F, Rossignol P, Iraqi W. Extracellular matrix fibrotic markers in heart failure. *Heart Fail Rev*. 2010; 15:319–329.

18. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann. Intern. Med.* 2003; 139:137–147.

19. Perkins NJ, Schisterman EF. The inconsistency of "optimal" cutpoints obtained using two criteria based on the receiver operating characteristic curve. *Am. J. Epidemiol.* 2006; 163:670–675.

20. Jugdutt BI. Ventricular Remodeling After Infarction and the Extracellular Collagen Matrix When Is Enough Enough? *Circulation*. 2003; 108:1395–1403.

21. Takino T, Nakamura M, Hiramori K. Circulating levels of carboxyterminal propeptide of type I procollagen and left ventricular remodeling after myocardial infarction. *Cardiology*. 1999; 91:81–86.

22. Cerisano G, Pucci PD, Sulla A, Tommasi M, Raspanti S, Santoro GM, Antoniucci D. Relation between plasma brain natriuretic peptide, serum indexes of collagen type I turnover, and left ventricular remodeling after reperfused acute myocardial infarction. *Am. J. Cardiol.* 2007; 99:651–656.

23. Manhenke C, Orn S, Squire I, Radauceanu A, Alla F, Zannad F, Dickstein K. The prognostic value of circulating markers of collagen turnover after acute myocardial infarction. *Int. J. Cardiol.* 2011; 150:277–282.

24. Jirmár R, Pelouch V, Widimský P, Capek J, Andel M, Průsa R, Pechová M. Influence of primary coronary intervention on myocardial collagen metabolism and left ventricle remodeling predicted by collagen metabolism markers. *Int Heart J*. 2005; 46:949–959.

25. Grothues F, Smith GC, Moon JCC, Bellenger NG, Collins P, Klein HU, Pennell DJ. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. *Am. J. Cardiol.* 2002; 90:29–34.

26. Jensen LT, Høst NB. Collagen: scaffold for repair or execution. *Cardiovasc. Res.* 1997; 33:535–539.

TABLES

TABLE 1. Baseline patient characteristics

Characteristics	All patients n = 206	PIIINP/ICTP ratio ≤ 1 µg/µg n = 99	> 1 µg/µg n = 107	p-value*
General				
Age (years)	57 ± 13	58 ± 15	55 ± 12	0.18
Men	166 (81%)	76 (77%)	90 (84%)	0.18
Body mass index (kg/m²)	27.3 ± 4.7	27.4 ± 4.8	27.3 ± 4.7	0.98
Hypertension	75 (36%)	39 (39%)	36 (34%)	0.39
Diabetes	37 (18%)	16 (16%)	21 (20%)	0.52
Hypercholesterolemia	75 (36%)	33 (33%)	42 (39%)	0.38
Current smokers	98 (48%)	43 (43%)	55 (51%)	0.25
Myocardial infarction				
Killip class ≥ 2	64 (31%)	30 (30%)	34 (32%)	0.82
CPK Peak (UI/l)	2258 (1450 - 3984)	2678 (1369 - 4256)	2133 (1531 – 3262)	0.19
Multivessel disease	81 (41%)	38 (40%)	43 (41%)	0.85
Initial reperfusion				
Primary PCI	158 (77%)	72 (73%)	86 (80%)	0.19
Thrombolysis	23 (11%)	15 (15%)	8 (7%)	0.081
No reperfusion	25 (12%)	12 (12%)	13 (12%)	1.00
PCI during hospitalization	179 (88%)	82 (84%)	97 (92%)	0.088
eGFR (ml/min/1.73m²)	84 ± 23	81 ± 25	88 ± 20	0.026
Baseline hemodynamic				
Heart rate (bpm)	71 ± 14	72 ± 13	70 ± 14	0.20
Systolic BP (mmHg)	110 ± 16	109 ± 18	110 ± 14	0.89
Diastolic BP (mmHg)	63 ± 11	61 ± 12	64 ± 10	0.036
Mean BP (mmHg)	78 ± 11	77 ± 12	79 ± 10	0.14
LVEDV (ml)	100 ± 29	98 ± 30	102 ± 29	0.29
LVESV (ml)	51 ± 22	51 ± 24	51 ± 19	0.52

LVEF (%)	50 ± 9	49 ± 9	50 ± 8	0.59
LVEF ≤ 45%	61 (30%)	28 (28%)	33 (31%)	0.69
Medications at discharge				
Aspirin	204 (99%)	98 (99%)	106 (99%)	0.96
Clopidogrel	199 (97%)	96 (97%)	103 (96%)	0.78
Beta-blockers	202 (98%)	97 (98%)	105 (98%)	0.94
ACE inhibitors	200 (97%)	96 (97%)	104 (97%)	0.92
Mineralocorticoid receptor antagonists	67 (33%)	35 (35%)	32 (30%)	0.40
Diuretics	48 (23%)	28 (28%)	20 (19%)	0.10
Statins	196 (95%)	93 (94%)	103 (96%)	0.44
Biomarkers at 1 month				
Cardiac troponin I ≥ 0.05 µg/l	36 (19%)	24 (25%)	12 (13%)	0.034
BNP (ng/l)	86 (51 - 181)	99 (56 - 219)	79 (44 - 145)	0.036
CRP (mg/l)	1.4 (0.7 - 3.4)	1.5 (0.7 - 4.4)	1.3 (0.6 - 2.8)	0.13
PINP (µg/l	36.9 (30.8 – 45.1)	35.5 (29.9 – 49.7)	37.9 (31.8 - 44.1)	0.57
PIIINP (µg/l)	5.21 (3.88 - 6.78)	4.03 (3.45 - 4.98)	6.28 (5.23 - 7.70)	< 0.0001
ICTP (µg/l)	4.76 (4.07 - 6.08)	5.29 (4.51 - 7.11)	4.45 (3.69 - 5.16)	< 0.0001
PIIINP/ICTP ratio	1.02 (0.80 - 1.34)	0.79 (0.64 - 0.91)	1.34 (1.13 - 1.70)	-

*p-value: from the Mann-Whitney test or the Chi-Square test as appropriate

ACE: angiotensin conversing enzyme; BNP: brain natriuretic peptide; BP: blood pressure; CPK: creatine phosphokinase; CRP: C reactive protein; eGFR: estimated glomerular filtration rate; ICTP: type 1 collagen telopeptide; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESV: left ventricular end-systolic volume; Mean BP: mean arterial pressure (Lian formula); PINP: aminoterminal propeptide of type I procollagen; PIIINP: aminoterminal propeptide of type III procollagen; PCI: primary percutaneous intervention.

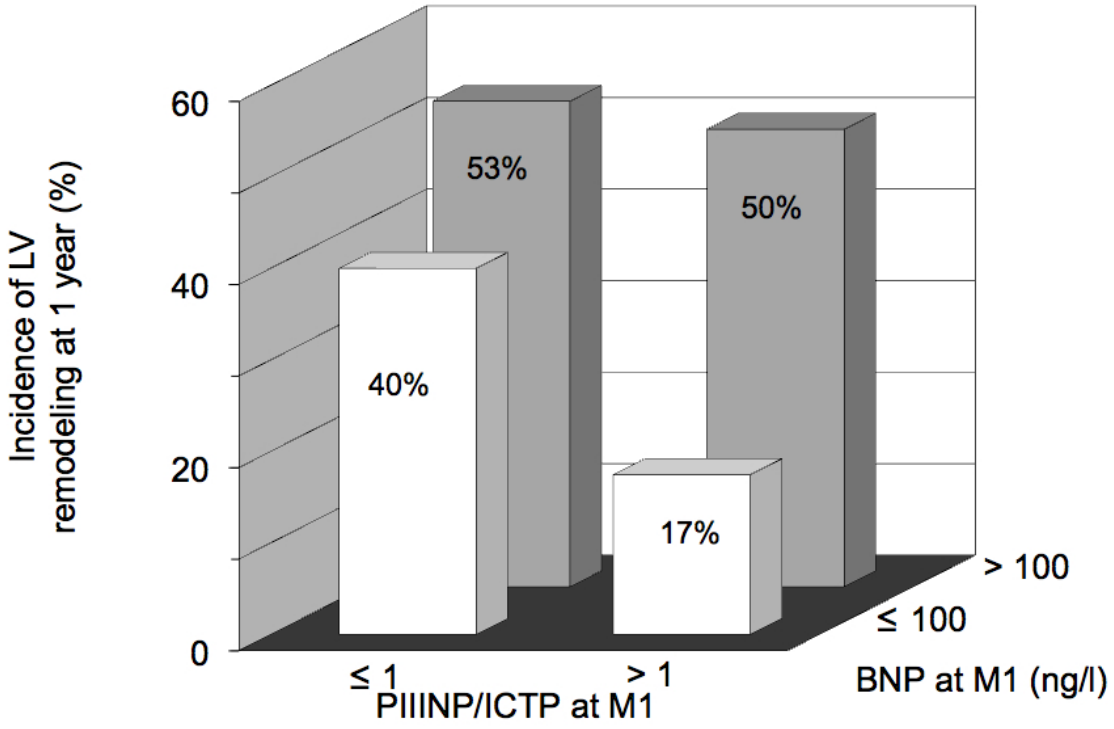
TABLE 2. Association of echocardiographic and biomarker features with left ventricle remodeling > 20% at 12 months as dependent variable, using univariate logistic regression analysis.

Covariate	n/N	r^2	c	OR (95%CI)	p-value
Discharge					
LVEF (per 5%)	79/206	0.053	0.642	0.75 (0.62 - 0.89)	0.001
eGFR (per 10 units)	79/205	<0.0001	0.497	0.99 (0.88 - 1.12)	0.89
1 month					
BNP (per $\log_e$)	78/204	0.056	0.649	1.72 (1.24 - 2.37)	0.001
Cardiac troponin I ≥0.05 µg/l	78/203	0.023	0.563	2.19 (1.08 - 4.44)	0.030
CRP (per $\log_e$)	79/205	0.005	0.537	1.12 (0.91 - 1.39)	0.29
PINP (per $\log_e$)	78/205	0.0006	0.527	1.16 (0.52 - 2.58)	0.73
PIIINP (per $\log_e$)	79/206	0.005	0.542	0.69 (0.33 - 1.46)	0.33
ICTP (per $\log_e$)	79/206	0.019	0.588	2.10 (0.98 - 4.53)	0.058
PIIINP/ICTP ratio (per decreasing $\log_e$)	79/206	0.027	0.587	2.09 (1.11 - 3.95)	0.023
PINP/ICTP ratio (per $\log_e$)	78/205	0.009	0.538	0.66 (0.36 - 1.20)	0.17

n/N: number of patients with LV remodeling > 20%/total number, r^2: determination coefficient (part of variance explained), c: Harrell's c-statistic (probability to rightly predict LV remodeling > 20%), OR (95%CI): odds ratio (95% confidence interval).
BNP: brain natriuretic peptide (ng/l); CRP: C reactive protein (mg/l); eGFR: estimated glomerular filtration rate (4-variable MDRD formula, ml/min/1.73m²); ICTP: type 1 collagen telopeptide (µg/l); LVEF: left ventricular ejection fraction; PINP: aminoterminal propeptide of type I procollagen (µg/l); PIIINP: aminoterminal propeptide of type III procollagen (µg/l).

FIGURES

FIGURE 1: 3D histograms according to ROC-determined cutoffs for BNP and PIIINP/ICTP ratio



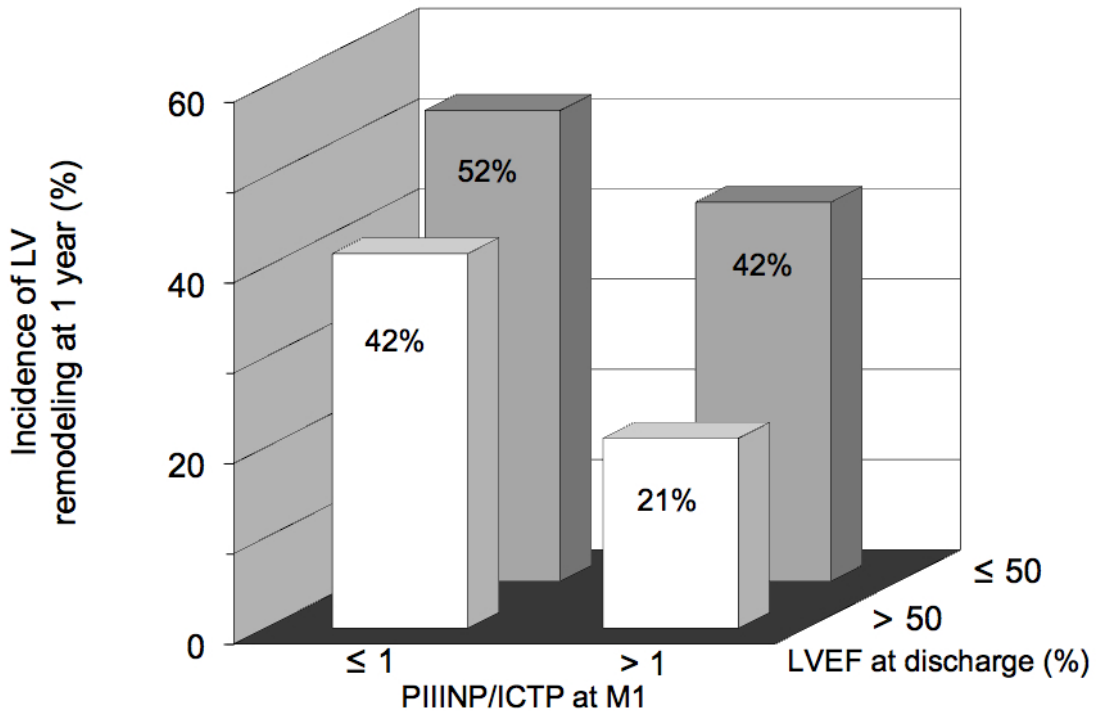
M12 remodeling: left ventricle end-diastolic volume increase > 20% at 12 months

Cutoff values determined from ROC curve (≅ medians): BNP ≤ vs. > 100 ng/l, PIIINP/ICTP ratio ≤ vs. > 1

Events/patients: 78/204

BNP: brain natriuretic peptide; PIIINP: aminoterminal propeptide of type III procollagen; ICTP: type 1 collagen telopeptide; ROC, receiver operating characteristic

FIGURE 2. 3D histograms according to ROC-determined cutoffs for LVEF and PIIINP/ICTP ratio



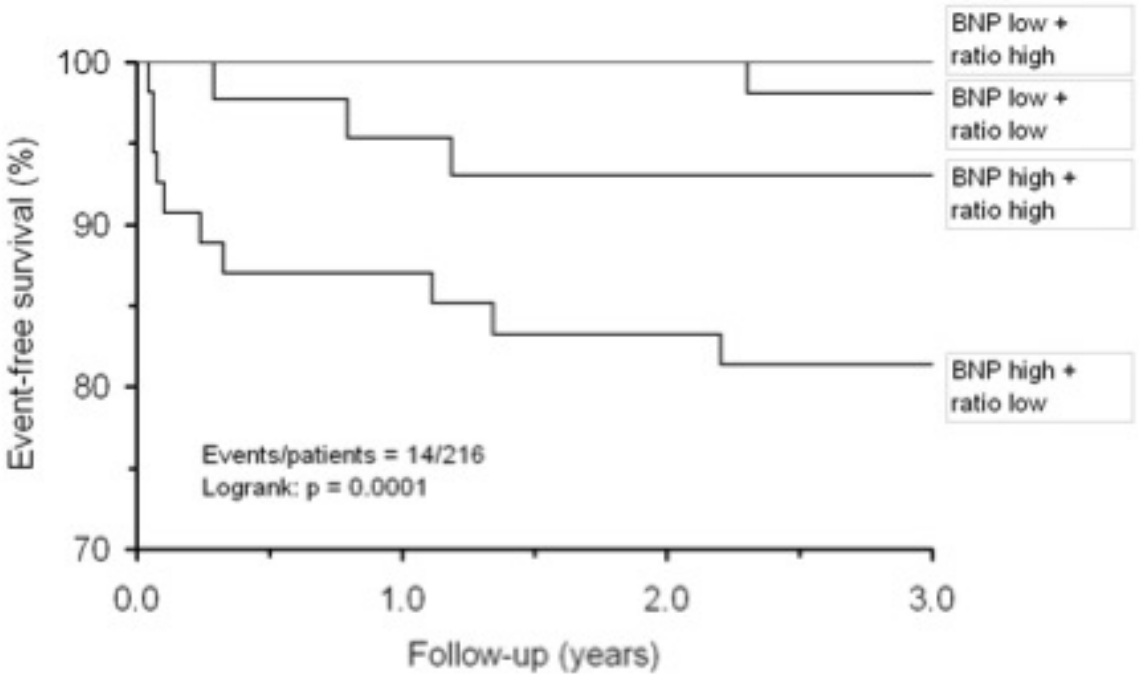
M12 remodeling: left ventricle end-diastolic volume increase > 20% at 12 months

Cutoff values determined from ROC curve (≅ medians): LVEF < vs. ≥ 50%, PIIINP/ICTP ratio ≤ vs. > 1 µg/µg

Events/patients: 79/206

LVEF: left ventricular ejection fraction; PIIINP: aminoterminal propeptide of type III procollagen; ICTP: type 1 collagen telopeptide; ROC, receiver operating characteristic

FIGURE 3. Kaplan-Meier curves showing cardiovascular death or hospitalization for worsening heart failure



Patients left at risk according to BNP and PIIINP/ICTP ratio combinations: number (survival)

low+high	66 (100%)	66 (100%)	66 (100%)	49 (100%)
low+low	53 (100%)	53 (100%)	52 (100%)	24 (98%)
high+high	43 (100%)	41 (95%)	40 (93%)	22 (93%)
high+low	54 (100%)	46 (87%)	44 (83%)	28 (81%)
all patients	216	206	202	123

Event: cardiovascular death or hospitalization for worsening heart failure

Strata: combinations of BNP high > 100 ng/l or low ≤ 100ng/l and PIIINP/ICTP ratio high > 1 or low ≤ 1 at one month

BNP: brain natriuretic peptide; PIIINP: aminoterminal propeptide of type III procollagen; ICTP: type 1 collagen telopeptide

4.3 Intérêt de l'éplérenone chez des patients à haut risque au stade C: IC à fonction systolique altérée au moins en classe II NYHA

Les antagonistes des récepteurs aux minéralocorticoïdes sont maintenant reconnus comme une thérapeutique de référence à visée anti-fibrotique cardiaque (recommandation de classe I, niveau de preuve A)[5]. Nous venons de montrer l'impact de la fibrose myocardique et l'importance des peptides collagéniques comme marqueurs pronostiques aux stades précoces de l'insuffisance cardiaque chez des patients asymptomatiques.

L'étude internationale EMPHASIS-HF effectuées chez 2737 patients aurait pu permettre de valider sur une large population le rôle de la fibrose et l'intérêt des peptides collagéniques. Nous pouvions avoir accès aux données de cette étude mais malheureusement aucune sérothèque n'a été constituée. L'hypothèse a donc été, d'étudier indirectement le rôle physiopathologique de la fibrose en explorant le rôle bénéfique d'une thérapeutique anti-fibrotique, l'éplérénone, antagoniste des récepteurs aux minéralocorticoïdes, chez des patients inclus dans EMPHASIS-HF et à haut risque de comorbidités mais aussi de remodelage.

Ce travail réalisé sur différents sous-groupes (âge > 75 ans, diabétiques, patients hypotendus et insuffisants rénaux modérés) pré-définis de l'étude EMPHASIS-HF[206] a permis de confirmer la sécurité d'utilisation d'un tel produit (absence de sur risque d'hospitalisation ou de mortalité par hyperkaliémie ou d'insuffisance rénale aiguë) ainsi que son efficacité.

4.3.1 *Safety and efficacy of eplerenone in patients at high-risk for hyperkalemia and/or worsening renal function: Analyses of EMPHASIS-HF study subgroups.*

Romain Eschalier, M.D., John J.V. McMurray, M.D., Karl Swedberg, M.D.,Ph.D., Dirk J vanVeldhuisen, M.D.,Ph.D., Henry Krum, M.B.,Ph.D., Stuart J. Pocock,Ph.D., Harry Shi, M.S., John Vincent, M.B.,Ph.D., Patrick Rossignol, M.D.,Ph.D., Faiez Zannad, M.D.,Ph.D., and Bertram Pitt, M.D. For the EMPHASIS-HF investigators.

Ce travail a fait l'objet d'une publication[207] dans le "Journal of the American College of Cardiology".

Accepted Manuscript

Safety and efficacy of eplerenone in patients at high-risk for hyperkalemia and/or worsening renal function: Analyses of EMPHASIS-HF study subgroups

Romain Eschalier, M.D. John J.V. McMurray, M.D. Karl Swedberg, M.D., Ph.D. Dirk J. van Veldhuisen, M.D., Ph.D. Henry Krum, M.B., Ph.D. Stuart J. Pocock, Ph.D. Harry Shi, M.S. John Vincent, M.B., Ph.D. Patrick Rossignol, M.D., Ph.D. Faiez Zannad, M.D., Ph.D. Bertram Pitt, M.D.

PII: S0735-1097(13)02512-6

DOI: 10.1016/j.jacc.2013.04.086

Reference: JAC 19030

To appear in: *Journal of the American College of Cardiology*

Received Date: 4 January 2013

Revised Date: 13 April 2013

Accepted Date: 15 April 2013

Please cite this article as: Eschalier R, McMurray JJV, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F, Pitt B, Safety and efficacy of eplerenone in patients at high-risk for hyperkalemia and/or worsening renal function: Analyses of EMPHASIS-HF study subgroups, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.04.086.

Safety and efficacy of eplerenone in patients at high-risk for hyperkalemia and/or worsening renal function: Analyses of EMPHASIS-HF study subgroups.

Brief Title: Eplerenone in high-risk patients.

Romain Eschalier, M.D.,[*,†] John J.V. McMurray,M.D.,[§] Karl Swedberg, M.D.,Ph.D.,[‖] Dirk J van Veldhuisen, M.D.,Ph.D.,[¶] Henry Krum, M.B.,Ph.D.,[#] Stuart J. Pocock,Ph.D.,[**] Harry Shi, M.S.,[††] John Vincent, M.B.,Ph.D.,[††] Patrick Rossignol, M.D.,Ph.D.,[*,‡‡,§§] Faiez Zannad, M.D.,Ph.D.,[*,‡‡,§§,‖‖] and Bertram Pitt, M.D.,[‡]. For the EMPHASIS-HF investigators.

[*]Centre d'Investigation Clinique Inserm CIC-P 9501, Centre Hospitalier Universitaire de Nancy ; †Clermont University, Université d'Auvergne, UMR6284, and the Department of Cardiology, Clermont-Ferrand, France; ‡ University of Michigan, School of Medicine, Ann Arbor; § The British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; ‖ the Department of Emergency and Cardiovascular Medecine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; ¶ the Department of Cardiology, Thorax Center, University Medical Center, Groningen, the Netherlands; # the Department of Epidemiology and Preventive Medecine, Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, VIC, Australia; **the Depatment of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom; ††Pfizer, New York; ‡‡ INSERM, U1116, Nancy, F-54000 France;§§ Université de Lorraine, Nancy, F-54000 France; ‖‖ Centre Hospitalier Universitaire de Nancy, department of Cardiology, France

Total word count: 4412

Disclosure: Supported by Pfizer. JJMM: grant support from the Eugene Braunwald Endowment for the Advancement of Cardiovascular Discovery and Care. HK: travel reimbursements from Pfizer. PR: received travel grants from Pfizer SP: receiving consulting fees from Servier, Amgen, AstraZeneca, and Novartis. HS and JV: employees of Pfizer and receiving stock options and travel reimbursements from Pfizer. FZ: fees for serving on the board of Boston Scientific; consulting fees from Novartis, Takeda, Astra-Zeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; and speaker's fees from Pfizer and AstraZeneca. BP: fees for serving on the board of Novartis; consulting fees from Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, BG Medicine, Nile Therapeutics, Merck, Forest Laboratories, and Novartis, grant support from Forest Laboratories and Novartis, and stock options from Relypsa, BG Medicine, Nile Therapeutics, and Aurasenc. No other potential conflict of interest relevant to this article was reported.

Address for correspondence: Faiez Zannad, CIC Inserm, Institut Lorrain du Cœur et des Vaisseaux. 4, rue du Morvan, 54500 Vandoeuvre-lès-Nancy-France
Tel: +33 3 83 15 73 22; Fax: +33 3 83 15 73 24; e-mail: f.zannad@chu-nancy.fr

ABSTRACT

Objectives. We investigated the safety and efficacy of eplerenone in patients at high-risk for hyperkalemia or worsening renal function (WRF) in EMPHASIS-HF, a trial which enrolled patients aged at least 55 years with heart failure and reduced ejection fraction (HF-REF), in NYHA functional class II and with an eGFR>30ml/min/1.73m^2 and serum potassium <5.0 mmol/l. Patients were receiving optimal therapy and most had been hospitalized for a cardiovascular reason within 180 days of inclusion.

Background. Underuse of eplerenone in patients with HF-REF may be due to fear of inducing hyperkalemia or WRF in high-risk patients.

Methods. This was a pre-specified analysis of subgroups of patients at high-risk of hyperkalemia or WRF (patients ≥75years, with diabetes, with eGFR<60ml/min/1.73m^2, and with systolic blood pressure <median of 123 mmHg), examining the major safety measures (potassium >5.5, >6.0 and <3.5mmol/l; hyperkalemia leading to study-drug discontinuation or hospitalization; and hospitalization for WRF) as well as the primary outcome (hospitalization for HF or cardiovascular mortality).

Results. In all high-risk subgroups, patients treated with eplerenone had an increased risk of potassium >5.5mmol/l but not of potassium >6.0mmol/l, and of hospitalization for hyperkalemia or discontinuation of study medication due to adverse events. Eplerenone was effective in reducing the primary composite endpoint in all sub-groups.

Conclusions. In patients with chronic HF-REF, in NYHA class II and meeting specific inclusion and exclusion criteria, including an eGFR >30ml/min/1.73m^2 and potassium <5.0 mmol/l, eplerenone was both efficacious and safe when carefully monitored, even in subgroups at high-risk of developing hyperkalemia or WRF.

Clinical trial ID: EMPHASIS-HF Study; NCT00232180

Key words: safety; efficacy; eplerenone; elderly; diabetes; chronic kidney disease

ABBREVIATIONS LIST

ACE-I: angiotensin converting enzyme inhibitor
ARB: angiotensin receptor blocker
BB: beta-adrenergic receptor blocking agent
(S) (D) BP: (systolic) (diastolic) blood pressure
CKD: chronic kidney disease
DM: diabetes mellitus
eGFR: estimated glomerular filtration rate
HF (REF): heart failure (with a reduced left ventricular ejection fraction)
MR (As): mineralocorticoid receptor (antagonists)
WRF: worsening renal function

INTRODUCTION

Mineralocorticoid receptor antagonists (MRAs) added to standard therapy including an angiotensin converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) and a beta adrenergic receptor blocking agent (BB) reduce mortality as well as hospitalization for heart failure (HF) in patients with a reduced left ventricular ejection fraction (HF-REF), irrespective of the severity of symptoms (1, 2), and in patients with reduced left ventricular ejection fraction and symptoms of HF after myocardial infarction (3). Mineralocorticoid receptor antagonists, therefore, have a pivotal place in the management of HF-REF (4) but, in comparison to ACE-I (or ARBs) and BBs, their use remains suboptimal (5). The reluctance of many clinicians to use a MRA in patients with HF-REF may in part be due to the belief that the large clinical trials [i.e. RALES (1), EPHESUS (3) and EMPHASIS-HF (2)] largely excluded high-risk patients, particularly those susceptible to hyperkalemia, worsening renal function (WRF) or both.

The aim of this analysis was to evaluate the safety and efficacy of the MRA eplerenone (25-50 mg/day) in pre-specified high-risk subgroups of this type, namely patients aged ≥ 75 years, with diabetes mellitus, chronic kidney disease (CKD) (i.e. an eGFR < 60 ml/min/1.73m^2), and SBP < median (123mmHg).

METHODS

The design (6) and results (2) of EMPHASIS-HF have been published.

Patients selection

Patients included were at least 55 years of age; in NYHA class II; had a left ventricular ejection fraction < 30% (or if between 30-35%, the QRS duration had to be > 130 milliseconds); were treated with the recommended or maximally tolerated dose of an ACE-I or an ARB and a BB (unless contraindicated) and had been hospitalized for a cardiovascular reason within the past 6

months (or had a B-type natriuretic peptide [BNP] level > 250 pg/ml or N-Terminal -pro-BNP > 500 pg/ml in males and 750 pg/ml for females).

Patients with an eGFR < 30 ml/min/1.73 m^2, need for a potassium sparring diuretic, or any other significant comorbid condition were excluded.

All trial endpoints, including hospitalization for WRF and for hyperkalemia were pre-specified and adjudicated by an independent Critical Event Committee. Each center's Ethics Committee approved the trial and all patients provided written informed consent.

Study procedure

Eplerenone or matching placebo was started at a dose of 25 mg once daily (or if the eGFR was 30-49 ml/min/1.73m^2, at a dose of 25 mg every other day) and increased to 50 mg once daily at 4 weeks, provided the serum potassium was no more than 5.0 mmol/l (or if the eGFR was 30-49 ml/min/1.73m^2 at baseline to 25 mg daily). Thereafter, the serum potassium was measured every 4 months and investigators were instructed to reduce the dose of the study drug if the serum potassium was 5.5 to 5.9 mmol/l and to withhold the study drug if the serum potassium was 6.0 mmol/l or more. Serum potassium was checked within 72 hours of stopping study drug and restarted only if the serum potassium was < 5.0 mmol/l. Serum potassium was measured at screening visit, Week 1, Week 4, every 4 months from Month 5 to Month 37, and every 6 months starting at Month 42 until the patient's final visit.

High-risk Subgroups

The pre-specified high-risk subgroups were patients ≥ age 75 years, those with diabetes mellitus, CKD (i.e. an eGFR < 60 ml/min/1.73m^2) and subjects with a SBP < 123 mmHg (median) at baseline.

Study outcomes

The pre-specified safety outcomes included serum potassium > 5.5, > 6.0 and < 3.5 mmol/l; hyperkalemia leading to study drug discontinuation; hospitalization for hyperkalemia and hospitalization for WRF; change in eGFR, as well as the primary efficacy outcome (hospitalization for HF or death from cardiovascular causes), were also reported.

Statistical analysis

The criteria for high-risk subgroups were pre-specified in the statistical analysis plan. The following data are summarized by study-treatment for each of the high-risk subgroups.

1. Demographics, medical history and relevant baseline laboratory measurements and medications (summarized using descriptive statistics).
2. Hospitalizations for hyperkalemia, and for WRF were analyzed using Cox proportional hazards models. The incidence of serum potassium above or below the pre-specified thresholds during the study were compared using Fisher's Exact Test. Change in eGFR between baseline and the final visit was analyzed using an ANCOVA model with baseline eGFR as a covariate. We also examined for interactions between baseline subgroup and the effect of treatment on potassium and eGFR using the Zelen's Test and the ANCOVA model including the interaction term, respectively.

   The adverse event data and study medication data including percent of subjects on highest dose (50 mg QD) and mean dose at Month 5 visit, and subject discontinuation are also summarized. Statistical comparisons between treatment groups were performed using two-sample t-tests for mean dose at Month 5 visit, and Fisher's Exact test for study discontinuation due to adverse events (AE). The BP change from baseline is also presented by baseline SBP < median and ≥ median subgroups.

3. The efficacy analyses on the primary endpoint (death from cardiovascular causes or hospitalization for HF) are performed using a Cox proportional hazards models including treatment, subgroup, and the treatment-by-subgroup interaction. Additionally, the corresponding Kaplan-Meier plots are presented by subgroups.

Role of the funding Source

The sponsor (Pfizer) was responsible for data management and final data analysis. The writing committee had full access to all data and was responsible for the interpretation of the results, the development and writing of the manuscript, and the decision to submit for publication.

RESULTS

The baseline characteristics of those patients randomized to placebo or eplerenone in EMPHASIS-HF overall, and in the high-risk subgroups, are presented in table 1. There were no striking clinical differences between the different high-risk subgroups and the overall population, except those reflected by the defining characteristic of the subgroup.

At the month 5 visit, after completion of the dose-adjustment phase 61.3% of patients assigned to receive eplerenone in the overall study population were taking the highest dose (50 mg daily); the corresponding proportion in the overall placebo group was 66.3%. Among the patients in overall population taking the study drug at the month 5 visit, the mean (±SD) doses in the eplerenone and placebo groups, respectively, were 39.5±13.6 mg and 41.1±12.7 mg. Neither the proportion of patients taking the highest dose (except for patients with CKD), nor the mean dose of study drug at the month 5 visit differed between eplerenone and placebo groups in each high-risk subgroups. (Figure 1A).

At the trial cut-off date, in the overall population, the study drug had been stopped, due to adverse event (at least one adverse event leading to drug being stopped), in 188 patients (13.8%) receiving eplerenone and 222 patients (16.2%) receiving placebo.

The number of patients with study drug stopped due to adverse events was evenly distributed within and among the study high risk subgroups, respectively in patients with age ≥ 75 [60/330 (18.2%) in eplerenone *vs.* 62/327 (19.0%) in placebo], in patients with SBP <123mmHg [111/669 (16.6%) in eplerenone *vs.* 122/679 (18.0%) in placebo], in patients with CKD [70/436 (16.1%) in eplerenone *vs.* 105/471 (22.3%) in placebo] and in patients with diabetes mellitus [69/457 (15.1%) in eplerenone *vs.* 72/398 (18.1%) in placebo]. Interestingly in patients with CKD (eGFR < 60 ml/min/1.73m^2), there were fewer patients in eplerenone group who had their treatment stopped due to an adverse event or due to any other reason than in placebo group. (Figure 1B)

The principal safety outcomes, change in eGFR and the primary efficacy outcome in the overall EMPHASIS-HF population and in each of the high-risk subgroups are summarized in table 2 and figure 2.

Safety *Outcomes*

Serum potassium > 5.5 mmol/l and > 6.0 mmol/l occurred preferentially during the first 18 months after study drug (eplerenone and placebo) initiation. After initiation of the study drug, a serum potassium > 5.5 mmol/l occurred at a median of 162.5 (range 4 – 1032) days in the eplerenone group compared with 235.0 (7 – 1008) days in the placebo group. Serum potassium >6.0mmol/l occurred at 276 (4 – 987) days in the eplerenone group and 235.0 (7 – 596) days in the placebo group.

Of 150 patients receiving eplerenone who had potassium > 5.0 mmol/L at Week 4, 141 (94.0%) did not have their study drug dose increased, as per protocol. For comparison, of 94 patients receiving placebo who had potassium > 5.0 mmol/L at Week 4, 83 (88.3%) did not have their study drug dose increased.

Patients ≥ 75 years

There was an increase in the proportion of older patients with a follow-up potassium > 5.5 mmol/l in those treated with eplerenone compared with placebo - 40(12.4) *vs.* 21(6.6), p=0.02 - but there was no difference in the proportion with a potassium > 6.0 mmol/l - 7(2.2) *vs.* 4(1.3), (p=0.55). There was no increase in any other safety outcome with eplerenone. However, the reduction in SBP between baseline and the final visit was greater in the eplerenone group - -4.75(18.8) *vs.* -0.70(16.5) mmHg, p=0.03 - compared to placebo group.

Furthermore, age (< 75 *vs.* ≥ 75 years) did not modify the effect of eplerenone on the risk of severe hyperkalemia (interaction p-value: p=0.64) or of change in eGFR from baseline to final visit (interaction p-value: p=0.5071).

Patients with diabetes mellitus

There was an increase in the incidence of potassium > 5.5 mmol/l with eplerenone in patients with diabetes - 63(14.1) *vs.* 33(8.5) on placebo, p=0.01. However, none of the other safety outcomes were increased in the eplerenone group, especially in the proportion with a serum potassium > 6.0 mmol/l - 17(3.8) *vs.* 8(2.1) on placebo, p=0.16 - and no more patients discontinued eplerenone for hyperkalemia in diabetes *vs.* no-diabetes patients (interaction p-value: p=0.12).

Patients with CKD (i.e. an eGFR < 60 ml/min/1.73m^2)

There was an increase in the incidence of potassium > 5.5 mmol/l with eplerenone in patients with CKD - 70(16.6) *vs.* 43(9.3) on placebo, p=0.002. There was no increase in any other safety outcome with eplerenone, including in the proportion with a serum potassium > 6.0 mmol/l - 8(1.9) *vs.* 15(3.3) on placebo, p=0.29.

Furthermore, there was actually a decrease in incident potassium > 6.0 mmol/l - 8(1.9) *vs.* 25(2.74), p=0.01 - but an increase in hyperkalemia leading to treatment discontinuation - 5(1.15) *vs.* 10(1.08), p=0.01 - in eplerenone patients with CKD compared to patients without CKD.

Patients with below median systolic blood pressure (SBP < 123mmHg)

There was an increase in the incidence of potassium > 5.5 mmol/l in patients with a SBP <123 mmHg - 72(10.9) *vs.* 48(7.3) on placebo, p=0.02. There was no increase in any other safety outcome with eplerenone, especially in the proportion with a serum potassium >6.0 mmol/l - 14(2.1) vs. 16(2.4) on placebo, p=0.85. Interestingly, there was no increase in the incidence of serum potassium > 5.5 nor > 6.0 mmol/l with eplerenone in patients in the lowest quartile of baseline SBP (< 110 mmHg) and in patients with SBP between lowest quartile and median (between 110 and 123 mmHg).

The mean decrease in SBP associated with the use of eplerenone in EMPHASIS-HF was 2 mmHg overall. In patients with a SBP below the median of 123 mmHg, SBP pressure increased on average by 4.96 (16.0) mmHg in the eplerenone group *vs.* 5.98 (16.2) mmHg in the placebo group (p=0.19). In patients with SBP ≥ median (123 mmHg) there was a significantly higher decrease in SBP in the eplerenone group as compared to the placebo group [-9.6(16.8) *vs.* -6.27(15.9) mmHg, p<0.001].

Furthermore, SBP (< 123 *vs.* ≥ 123 mmHg) did not modify the effect of eplerenone on the risk of severe hyperkalemia (p=0.10) or of change in eGFR from baseline to final visit (p=0.66).

Primary efficacy outcome

Eplerenone was effective at reducing the risk of cardiovascular death or HF hospitalization in the high-risk subgroups which is consistent with result in the overall, EMPHASIS-HF population – HR: 0.63 (0.54,0.74), p<0.001.

Correspondingly, the hazard ratio for the primary outcome in the eplerenone group as compared with the placebo group was 0.66 [(0.54,0.80), p<0.0001] in patients < 75 years, 0.72 [(0.58,0.88), p=0.002] in patients without diabetes, 0.69 [(0.56,0.86), p=0.0008] in patients without CKD and 0.68 [(0.53,0.87), p=0.002] in patients with SBP ≥ median. All interaction tests were not significant.

The hazard ratio for the primary outcome in the eplerenone group as compared with the placebo group was 0.66 [(0.49,0.88), p=0.005] in patients ≥ 75 years, 0.54 [(0.42,0.70), p<0.0001] in patients with diabetes, 0.62 [(0.49,0.79], p=0.0001] in patients with CKD and 0.63 [(0.51,0.79], p<0.0001] in patients with SBP < median (123mmHg). (Figure 2)

Moreover the hazard ratio for the primary outcome (hospitalization for HF and/or CV death) in the eplerenone group as compared with the placebo group was 0.63 [(0.44,0.89), p=0.009] in patients in the lowest quartile of baseline SBP < 25 percentile (<110 mmHg), and 0.64 [(0.48,0.84), p=0.001] in patients with SBP between the lowest and median (110 and 123 mmHg).

DISCUSSION

The present findings show that eplerenone, started at a dose of 25 mg and carefully up-titrated to 50 mg (mean dose 40 mg) as tolerated, has a favorable benefit-risk profile in carefully selected and monitored patients, even if at increased risk of renal dysfunction, hyperkalemia and hypotension because of advanced age, diabetes, CKD or low systolic blood pressure.

Specifically, the benefit of reduced incidence of cardiovascular death or heart failure hospitalization was preserved in all the high-risk subgroups studied without an increase in the risk of serious hyperkalemia and worsening renal function in any subgroup.

Older patients (≥ 75 years of age)

Aldosterone levels decrease with age (7). However, aldosterone is not the only natural ligand of mineralocorticoid receptors (MR). Cortisol is a very potent agonist of MRs, but in physiological conditions, the enzyme 11βHSD2 converts cortisol, to cortisone which does not activate the MR (8). Importantly, however, there is a decrease in the expression of this enzyme with age. Thus in the elderly, cortisol may be more active on MR in the vascular wall, in the renal tubule, and in the myocardium. There is also an increase in the expression of the MR with age in the vascular wall (9) which, in conjunction with the decrease in expression of 11βHSD2, suggests that MR signaling may be as or more important in the elderly than in younger patients.

Clinicians may also be concerned about the safety of adding a MRA to an ACE-I or ARB and a BB in the elderly. It was therefore of interest to note that both the mean dose and the percentage of patients attaining the highest dose of eplerenone at the month 5 visit was the same in older patients as in the overall EMPHASIS-HF population. Similarly, the frequencies of the pre-specified safety outcomes were generally similar in older patients and in patients less than 75 years old.

Diabetes Mellitus

Diabetes Mellitus is a major risk factor for the development of hyperkalemia (10) and renal failure. One postulated explanation for the increased risk of hyperkalemia in diabetes is hyporeninemic hypoaldosteronism. However, risks were not increased in diabetes (except modest hyperkalemia) suggesting that hyporeninemic hypoaldosteronism may be actually not

quite common in diabetes. Excess hyperkalemia might just be due to the associated CKD. Although the present data show that eplerenone is similarly beneficial in patients with diabetes than in those without, Eplerenone does not reduce new-onset of diabetes in this population (11). It is therefore reassuring that eplerenone appeared to be well tolerated and safe in the selected and carefully monitored patients with diabetes in EMPHASIS-HF (38% of which had concomitant CKD).

Chronic Kidney Disease

Aldosterone-induced kidney injury is likely to be multifactorial, including its effect on systemic blood pressure, renal vasculature, local inflammation, and fibrosis (12). In addition to the traditional pathway, in renal tubular epithelial cells, activation of MR in non-epithelial tissues has been shown to cause hypertrophy and fibrosis (13).

Patients with HF-REF and concomitant CKD (eGFR < 60ml/min/1.73m^2) are at increased cardiovascular risk compared to those with preserved renal function. But they are less likely to be treated with RAAS blockers or to receive the target dose of these agents. However, several studies and reviews highlighted the benefit of the addition of MRAs to ACEI and/or ARB therapy in patients with proteinuric kidney disease to significantly reduce proteinuria, without causing significant hyperkalemia or worsening renal function (14, 15). Furthermore, Vardeny *et al.* recently showed in a sub-study of RALES that the absolute benefit of spironolactone was greatest in patients with reduced eGFR (eGFR < 60ml/min/1.73m^2) (16).

It was therefore especially reassuring that while there was an increase in the frequency of mild hyperkalemia (serum potassium > 5.5 mmol/l) in patients randomized to eplerenone, there was also no significant increase in the frequency of serious hyperkalemia or WRF.

It is our view, therefore, that patients with HF-REF and concomitant CKD, meeting the inclusion and exclusion criteria of EMPHASIS–HF, should, cautiously be given a trial of eplerenone beginning at a dose of 25 mg/day, with serial monitoring of serum potassium in an attempt to reduce the particularly high mortality and morbidity in these patients. It must however be emphasized that, although this analysis was performed for patients with eGFR < 60 ml/min/1.73m², those with an eGFR < 30 ml/min/1.73m² and those with a baseline serum potassium > 5.0 mmol/l were excluded from the study. Furthermore, those with eGFR 30-49 ml/min/1.73m² had a different and more cautious dosing regimen (eplerenone was started at a dose of 25 mg every other day and increased to 25 mg daily 4 weeks, provided the serum potassium was no more than 5.0 mmol/l).

Systolic Blood Pressure below median (< 123 mmHg)

Hypotension is a particular concern in patients with HF-REF who often have an intrinsically low systolic blood pressure and usually an indication for three or more blood pressure-lowering drugs (17).These concerns are greatest in the elderly who are at risk of orthostatic hypotension leading to falls and loss of consciousness.

As in the other pre-specified high-risk subgroups in this analysis the use of eplerenone did not result in any significant increase in the incidence of serious hyperkalemia, or WRF. Interestingly there was no clinically significant decrease of SBP in those with SBP < median.

This experience with eplerenone 25-50 mg/daily in the various high-risk subgroups reported here is in contrast to that reported over the last several years from many centers who noted frequent intolerance of MRAs, in part related to a high incidence of hyperkalemia, acute renal failure or both. For example after RALES (1) Juurlink *et al.* (18) noted an increased incidence of hospitalization for hyperkalemia in Ontario in patients with HF treated with spironolactone

(patients were on average 13 years older than in RALES). More recently the TIME-CHF investigators (19) found that the use of spironolactone > 25 mg/day in patients > 60 years of age was associated with a more than 25% incidence of mild hyperkalemia (> 5.5 mmol/l). A recent study from the Cleveland Clinic, evaluating the use of MRAs in patients admitted with HF after the results of EMPHASIS-HF (2), noted a high incidence (40%) of MRA (spironolactone in 90% of cases) discontinuation during hospitalization (20).

One explanation for the high incidence of hyperkalemia and/or WRF, as well as intolerance associated with the use of a MRA, in these patients is that many clinicians have used spironolactone in the dosing regimen used in RALES (12.5-50 mg/day) in patients with HF and mild symptoms such as those in EMPHASIS-HF (19, 21). These doses may not be associated to the same risk/benefit than observed with eplerenone 25-50 mg in EMPHASIS-HF. Furthermore all these studies included both patients with HF with preserved ejection fraction, in whom MRAs were not recommended, as well as those with HF-REF. Importantly patients included in studies cited above were on average older, with more severe CKD (patients with eGFR < 30 ml/min/1.73m^2 were included in TIME-CHF) and received higher MRA doses than in RALES or EMPHASIS-HF (22). Finally patients may have also taken nonsteroidal anti-inflammatory agents, other potassium-sparing diuretics and potassium supplements in these studies, drugs which increase the risk of developing serious hyperkalemia and/or WRF. Those patients were excluded from EMPHASIS-HF study. Furthermore, patients included in EMPHASIS-HF trial, as in other trials cited above, had to be on optimal ACEi/ARB therapy before enrolment, which may have selected out a population less likely to have hyperkalemia or WRF secondary to MRA, as compared to unselected patients reported in observational registries. It is appropriate to emphasize that our conclusions are limited to the EMPHASIS-HF type of patients and may not

apply to the patients at the highest risk for complications who were excluded from the study. The subsets evaluated in the current analysis represent high-risk subgroups, which were not excluded by the entry criteria. Importantly, surveillances of serum potassium and renal function were probably more closely made in patients included in EMPHASIS-HF study than in "real life" patients.

Based on the very low incidence rates of severe hyperkalemia (K > 6.0 mmol/l) and the sample sizes, the comparisons within subgroups are underpowered, and therefore, type II error cannot be excluded and the lack of statistical significance should not be portrayed as categorical proof that patients on eplerenone have no difference in risk (either greater or smaller) than placebo patients. However, two subgroups showed a greater percentage for eplerenone and two showed a greater percentage for placebo.

CONCLUSION

The excellent benefit-to-risk ratio of eplerenone in the subgroups in this analysis at high-risk for developing hyperkalemia and/or worsening renal function with an excellent safety and tolerance combined with a substantial reduction of the combined endpoint of cardiovascular mortality and hospitalization for HF, presents compelling evidence for its use in all patients with HF-REF meeting the inclusion and exclusion criteria of EMPHASIS-HF. Even so serum potassium and renal function have to be carefully monitored in these patients strictly selected to benefit from MRAs.

REFERENCES

1. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N. Engl. J. Med 1999;341(10):709–717.

2. Zannad F, McMurray JJV, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. N. Engl. J. Med. 2011;364(1):11–21.

3. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N. Engl. J. Med. 2003;348(14):1309–1321.

4. McMurray JJV, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur. J. Heart Fail. 2012;14(8):803–869.

5. Albert NM, Yancy CW, Liang L, et al. Use of aldosterone antagonists in heart failure. JAMA 2009;302(15):1658–1665.

6. Zannad F, McMurray JJV, Drexler H, et al. Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). Eur. J. Heart Fail. 2010;12(6):617–622.

7. Weidmann P, De Myttenaere-Bursztein S, Maxwell MH, De Lima J. Effect on aging on plasma renin and aldosterone in normal man. Kidney Int. 1975;8(5):325–333.

8. Henschkowski J, Stuck AE, Frey BM, et al. Age-dependent decrease in 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2) activity in hypertensive patients. Am. J. Hypertens. 2008;21(6):644–649.

9. Krug AW, Allenhöfer L, Monticone R, et al. Elevated mineralocorticoid receptor activity in aged rat vascular smooth muscle cells promotes a proinflammatory phenotype via extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase and epidermal growth factor receptor-dependent pathways. Hypertension 2010;55(6):1476–1483.

10. Johnson ES, Weinstein JR, Thorp ML, et al. Predicting the risk of hyperkalemia in patients with chronic kidney disease starting lisinopril. Pharmacoepidemiol Drug Saf 2010;19(3):266–272.

11. Preiss D, Van Veldhuisen DJ, Sattar N, et al. Eplerenone and new-onset diabetes in patients with mild heart failure: results from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF). Eur. J. Heart Fail. 2012;14(8):909–915.

12. Ma TK-W, Szeto C-C. Mineralocorticoid receptor antagonist for renal protection. Ren Fail 2012;34(6):810–817.

13. Funder JW. Aldosterone and mineralocorticoid receptors: orphan questions. Kidney Int. 2000;57(4):1358–1363.

14. Bianchi S, Bigazzi R, Campese VM. Long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int. 2006;70(12):2116–2123.

15. Bomback AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors or angiotensin receptor blockers in CKD: a systematic review. Am. J. Kidney Dis. 2008;51(2):199–211.

16. Vardeny O, Wu DH, Desai A, et al. Influence of Baseline and Worsening Renal Function on Efficacy of Spironolactone in Patients With Severe Heart Failure. Journal of the American College of Cardiology 2012;60(20):2082–2089.

17. Mak G, Murphy NF, Ali A, et al. Multiple neurohumoral modulating agents in systolic dysfunction heart failure: are we lowering blood pressure too much? J. Card. Fail. 2008;14(7):555–560.

18. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N. Engl. J. Med. 2004;351(6):543–551.

19. Muzzarelli S, Maeder MT, Toggweiler S, et al. Frequency and predictors of hyperkalemia in patients ≥60 years of age with heart failure undergoing intense medical therapy. Am. J. Cardiol. 2012;109(5):693–698.

20. Chamsi-Pasha MAR, Dupont M, Tang WH. CONTEMPORARY ADMINISTRATION OF ALDOSTERONE RECEPTOR ANTAGONISTS IN PATIENTS HOSPITALIZED WITH CONGESTIVE HEART FAILURE AFTER EMPHASIS-HF. Journal of the American College of Cardiology 2012;59(13):E890.

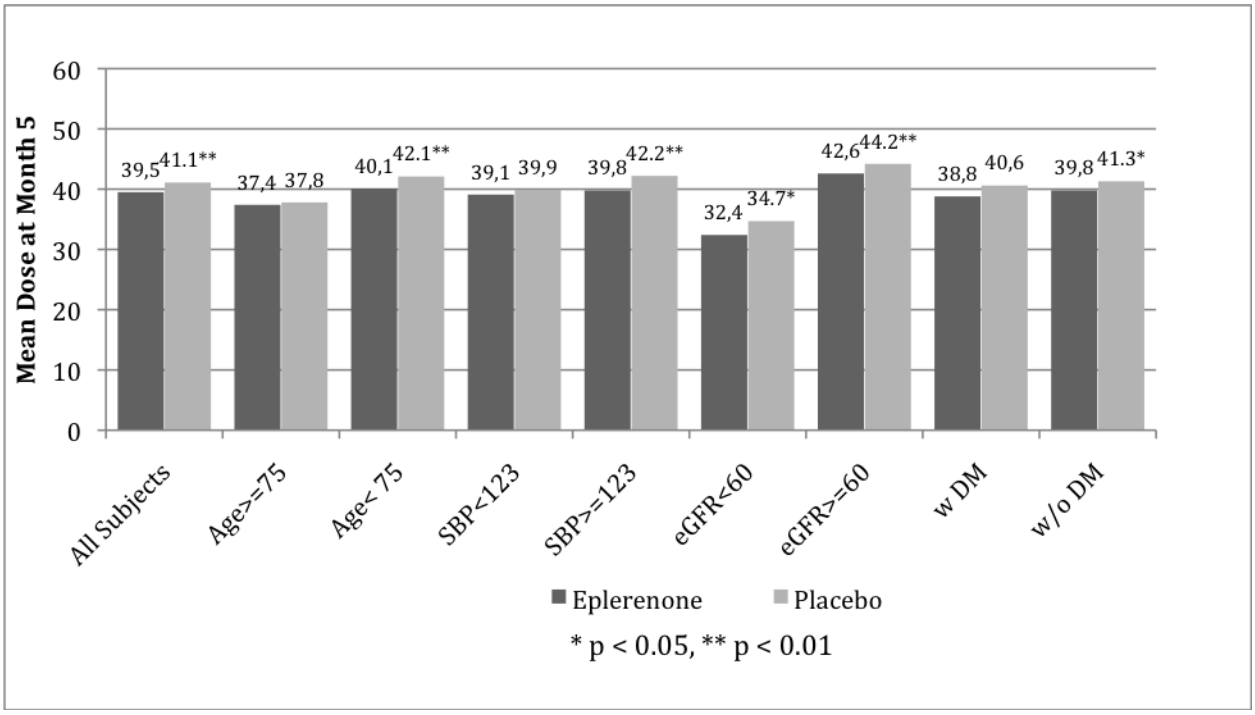
21. Pfisterer M, Buser P, Rickli H, et al. BNP-guided vs symptom-guided heart failure therapy: the Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) randomized trial. JAMA 2009;301(4):383–392.

22. McMurray JJV, O'Meara E. Treatment of heart failure with spironolactone--trial and tribulations. N. Engl. J. Med. 2004;351(6):526–528.

FIGURES

FIGURE 1.

1A: Mean dose of study drug at month 5 visit in overall study population and in each high-risk subgroup



1B: Discontinuation of study drug due to adverse event at month 5 visit in overall study population and in each high-risk subgroup

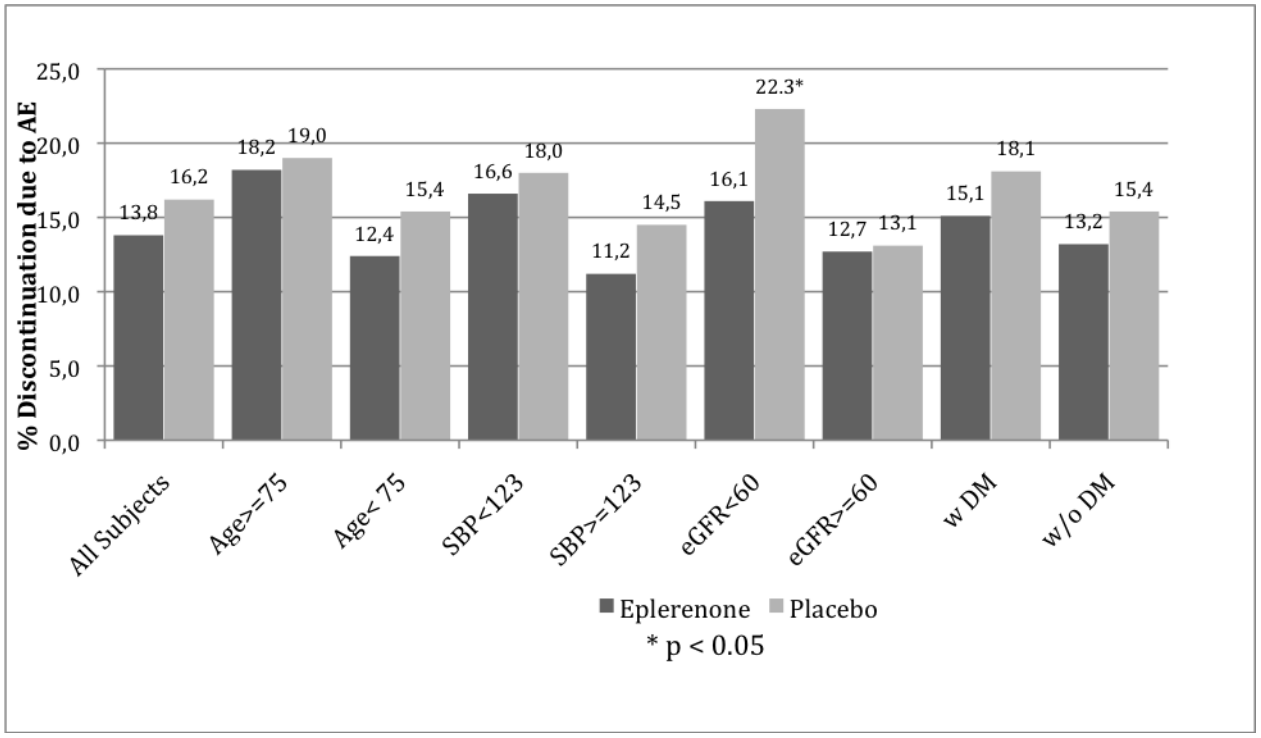
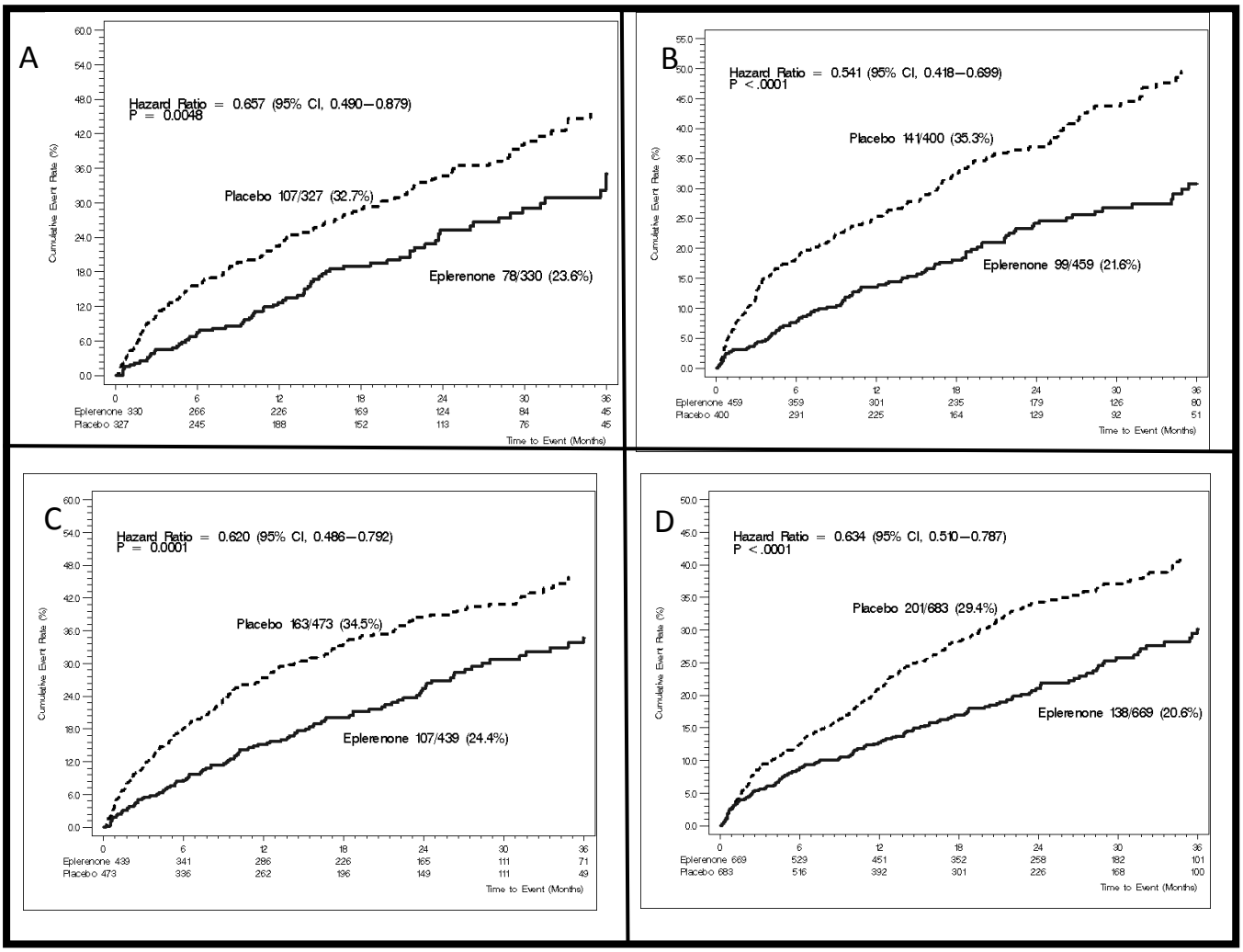


FIGURE 2. Cumulative Kaplan-Meier Estimates of the cumulative event rate (primary endpoint), according to high-risk subgroups.



Cumulative Kaplan-Meier Estimates of the cumulative event rate, according to high-risk subgroups (Panel A: ≥ 75 years old; Panel B: history of diabetes, Panel C: eGFR < 60 ml/min/1.73m^2, Panel D: Systolic blood pressure < median (123 mmHg).

TABLES

TABLE 1: Baseline characteristics

Characteristics	**EMPHASIS-HF study Population**		**Age ≥ 75 year's old**	**Diabetes mellitus**	**eGFR < 60 ml/min/1.73m^2**	**Baseline SBP ≤ median (123mm Hg)**
	Eplerenone group n=1364	**Placebo group n=1373**	**Eplerenone group n=330**	**Eplerenone group n=459**	**Eplerenone group n=439**	**Eplerenone group n=682**
Age — yr	68.7 ± 7.7	68.6 ± 7.6	79.1 ± 3.5	68.1 ± 7.4	71.1 ± 7.5	68.2 ± 7.6
Female sex – no. (%)	309 (22.7)	301 (21.9)	78 (23.6)	103 (22.4)	119 (27.1)	148 (21.7)
Systolic	124 ± 17	124 ± 17	127.07 ± 17.1	125.23 ± 17.1	122.23 ± 16.9	110.51 ± 9.1
Diastolic	75 ± 10	75 ± 10	73.67 ± 10.5	74.64 ± 10.3	73.19 ± 10.9	69.32 ± 8.7
Left ventricular ejection fraction - %	26.2 ± 4.6	26.1 ± 4.7	26.72 ± 4.3	26.44 ± 4.7	26.39 ± 4.7	25.74 ± 4.8
Hospitailzation for heart failure – no. (%)	714 (52.3)	726 (52.9)	169 (51.2)	234 (51.0)	254 (57.9)	394 (57.8)
Hypertension — no. (%)	910 (66.7)	909 (66.2)	250 (75.8)	348 (75.8)	304 (69.2)	374 (54.8)
Myocardial infarction – no. (%)	686 (50.3)	695 (50.6)	188 (57.0)	249 (54.2)	241 (54.9)	352 (51.6)
Diabetes mellitus — no. (%)	459 (33.7)	400 (29.1)	97 (29.4)	459 (100.0)	167 (38.0)	211 (30.9)

Serum creatinine – mg/dl	1.14 ± 0.30	1.16±0.31	1.22 ± 0.3	1.17 ± 0.3	1.44 ± 0.3	1.16 ± 0.3
Estimated GFR — ml/min/1.73 m^2 of BSA	71.2 ± 21.9	70.4±21.7	63.99 ±20.0	69.27 ± 22.0	48.59 ±7.9	68.77 ± 20.7
Estimated GFR rate < 60 ml/min/1.73 m^2 - no. (%)	439 (32.2)	473 (34.5)	151 (45.8)	167 (36.4)	439 (100.0)	246 (36.1)
Serum potassium — mmol/liter	4.3 ± 0.4	4.3±0.4	4.30 ± 0.4	4.34 ± 0.4	4.36 ± 0.4	4.30 ± 0.4
Diuretic	1150 (84.3)	1176 (85.7)	286 (86.7)	408 (88.9)	400 (91.1)	592 (86.8)
ACE inhibitor	1068 (78.3)	1055 (76.8)	266 (80.6)	340 (74.1)	342 (77.9)	551(80.8)
ARB	261 (19.1)	266 (19.4)	85 (25.8)	138 (30.1)	124 (28.3)	166(24.3)
ACE inhibitor, ARB, or both	1282 (94.0)	1275 (92.9)	316 (95.8)	439 (95.6)	419 (95.4)	649(95.2)
Beta-blocker	1181 (86.6)	1193 (86.9)	286 (86.7)	399 (86.9)	387 (88.2)	587 (86.1)

TABLE 2: Primary outcome and major safety issues

Outcome	**EMPHASIS-HF study Population**		**Age ≥ 75 year's old**		**Diabetes mellitus**		**eGFR < 60 ml/min/1.73m^2**		**Baseline SBP < median (123mmHg)**	
	Eplerenone group n=1364	**Placebo group n=1373**	**Eplerenone group n=330**	**Placebo group n=327**	**Eplerenone group n=459**	**Placebo group n=400**	**Eplerenone group n=439**	**Placebo group n=473**	**Eplerenone group n=669**	**Placebo group n=683**
Hospitalization for heart failure or death for cardiovascular	249 (18.3)	356 (25.9)**	78 (23.6)	107 (32.7)**	99 (21.7)	141 (35.2)***	107 (24.4)	163 (34.5)***	138 (20.6)	201 (29.4)***
Serum K+ > 5.5 mmol/l	158/1336 (11.8%)	96/1340 (7.2%)***	40/322 (12.4)	21/318 (6.6)*	63/447 (14.1)	33/387 (8.5)**	70/422 (16.6)	43/461 (9.3)**	72/658 (10.9)	48/660 (7.3)*
Serum K+ > 6.0 mmol/l	33/1336 (2.5%)	25/1340 (1.9%)	7/322 (2.2)	4/318 (1.3)	17/447 (3.8)	8/387 (2.1)	8/422 (1.9)	15/461 (3.3)	14/658 (2.1)	16/660 (2.4)
Change in eGFR from baseline to final visit	-3.18 (18.4)	-1.29 (27.4)*	-5.29 (17.6)	-4.07 (15.4)	-4.94 (17.4)	-2.93 (18.9)	2.04 (17.0)	4.15 (14.9)	-1.31 (17.3)	-0.07 (17.5)

Difference between eplerenone and placebo groups within different subgroups: * $p \leq 0.05$; ** $p \leq 0.01$; ***$p \leq 0.0001$.

5 DISCUSSION ET PERSPECTIVES

5.1 DISCUSSION

Ces travaux ont permis de montrer la pertinence clinique des dosages sanguins des peptides collagéniques tout au long du processus de l'insuffisance cardiaque : du stade asymptomatique aux stades symptomatiques.
Nous avons mis en évidence, à travers l'expression des peptides collagéniques que :

1/ des patients asymptomatiques ayant une obésité abdominale présentent un remodelage cardiaque précoce tant structurel que fonctionnel (augmentation de la masse ventriculaire gauche, dysfonction diastolique associée au PIIINP) : R2C2 Study.

2/ le ratio PIIINP/ICTP ≤ 1, mesuré 1 mois après un infarctus, est indépendamment associé à la survenue d'un remodelage ventriculaire gauche à 1 an et améliore la prédiction de survenue d'évènements cardiovasculaires (décès cardiovasculaires et hospitalisation pour décompensation cardiaque) à 3 ans : REVE-2 study.

3/ l' antagoniste des récepteurs aux minéralocorticoïdes (éplérénone), traitement anti-fibrotique par excellence, est efficace et sûr chez des patients à hauts risques de remodelage et de complications : EMPHASIS-HF study.

Ceci confirme l'impact majeur du turnover de la matrice extracellulaire vers le dépôt de fibrose myocardique dans cette population quelque soit le stade d'évolution.

5.1.1 *Pourquoi choisir des biomarqueurs?*

Les différentes données physiopathologiques issues des études animales et humaines ont permis de mieux appréhender les mécanismes responsables du remodelage ventriculaire gauche dans l'insuffisance cardiaque. La fibrose est alors apparue comme

l'un des éléments centraux de ce remodelage et donc l'une des cibles thérapeutiques prioritaires. La fibrose myocardique est facilement évaluée chez l'animal par l'étude anatomopathologique des cœurs sacrifiés. Il était indispensable de pouvoir évaluer celle-ci chez l'homme de façon non invasive. C'est avec cet objectif que plusieurs équipes dont la nôtre ont décidé d'explorer la voie de différents biomarqueurs dont ceux de la matrice extracellulaire : les peptides collagéniques.

5.1.2 *Qu'est-ce-qu'un biomarqueur?*

L'impact des différentes pathologies cardiaques en terme de morbi-mortalité mais également de dépenses de santé a conduit les scientifiques a essayé d'améliorer la détection, la prévention, la stratification du risque et la prise en charge à l'échelon individuel de ces nombreux patients. Il apparaît nécessaire d'avoir une méthode non invasive qui permette une évaluation fiable de la physiopathologie mais également de son pronostic ou de reprise au traitement sous forme de critères de substitution (« surrogate endpoints »).

Le terme « biomarqueur » renvoie habituellement à des molécules dans le sang ou les urines. Mais celui-ci est défini pour la première fois en 2001 par un groupe de travail du NIH comme un « critère mesuré et évalué comme un inducteur de processus physiologiques normaux, de processus pathologiques ou de réponses pharmacologiques à une intervention thérapeutique »[208] que Vasan R.S. a précisé en 2006[209]. Le terme de biomarqueur peut donc faire référence à des molécules pouvant être dosées dans le sang, les urines ou un autre tissue mais également à des enregistrement obtenus du patient comme un électrocardiogramme, un Holter ECG ou tensionnel, ou à des examens d'imagerie (échocardiographie, IRM…).

Les biomarqueurs peuvent donc avoir différents rôles et une classification a été proposée[208]:

- « antecedent biomarkers » (identifie le risque de développer une pathologie)
- « screening biomarkers » (détecte une pathologie asymptomatique)

- « diagnosis biomarkers » (permet le diagnostic d'une pathologie)
- « staging biomarkers » (grade la sévérité de la pathologie)
- « prognostic biomarkers » (prédit l'évolution de la pathologie dont les récurrences mais également la réponse aux traitements entrepris)

Il faut distinguer 2 processus d'acceptation d'un biomarqueur[210]:

- la validation, qui consiste à analyser la méthode de mesure et ses caractéristiques mais aussi à déterminer les conditions validant la méthode de mesure (reproductibilité et précision).
- la qualification, qui est le processus prouvant une relation significative entre le biomarqueur, les processus biologiques et des critères d'évaluation clinique.

Le biomarqueur idéal n'existe pas mais celui-ci devrait être capable d'aider le clinicien a optimiser la pris en charge de son patient à tout le stade de la pathologie.

5.1.3 *Pourquoi choisir les peptides collagéniques?*

Notre choix s'est porté sur l'utilisation des peptides collagéniques car ils sont des marqueurs fiables et validés du dépôt de fibrose dans le myocarde. Ils ont en effet fait l'objet de nombreuses études permettant ainsi de répondre aux définitions proposées[208,209]. Malgré les limites explicitées précédemment (cf. partie 2.4.2.) les peptides collagéniques utilisés dans nos travaux ont montré leur intérêt comme pour appréhender la physiopathologie mais également pour prédire la réponse à différentes thérapeutiques employées. Ils sont d'ailleurs considérés commes les peptides collagéniques à privilégier[184].

Sur le plan physiopathologique, le turnover de la matrice extracellulaire, au même titre que l'hypertrophie myocytaire, l'inflammation ou l'activation des systèmes neuro-hormonaux est un élément majeur du développement d'un remodelage ventriculaire

gauche dans les différents types de cardiopathies. Il est à l'heure actuelle illusoire de vouloir étudier le remodelage ventriculaire sans évaluer la fibrose. Comme décrit précédemment les peptides collagéniques ont montré leur intérêt dans la compréhension des mécanismes de transition vers l'insuffisance cardiaque mais également leur intérêt à visée pronostique dans les cardiopathies hypertensives notamment.

Sur le plan thérapeutique, les différentes équipes ont essayé après avoir appréhendé le rôle central du dépôt de fibrose dans la physiopathologie de l'insuffisance cardiaque d'interagir avec cette fibrose afin de la faire régresser et ainsi d'améliorer le pronostic des patients. Le rôle délétère de l'aldostérone comme pro-fibrotique a été mis en évidence dans les modèles animaux[211,212], mais également chez l'homme[187,204].

Notre équipe a déjà mis en évidence que les antagonistes des récepteurs aux minéralocorticoïdes avaient un effet positif par une action anti-fibrotique sur le remodelage ventriculaire dans l'insuffisance cardiaque chronique et en post-infarctus immédiat[187,204]. Il a été démontré que des concentrations élevées de peptides collagéniques sont prédictrices d'augmentation de morbi-mortalité mais également que les patients qui tirent le plus grand bénéfice de ces thérapeutiques sont les patients les plus graves initialement[204] mais aussi ceux avec des taux de peptides collagéniques plus élevés (PIIINP)[187].

L'ensemble des données obtenues par ce travail nous conduit à envisager l'utilisation de cette classe thérapeutique dans différentes populations à risque ou atteintes d'IC tout en prévoyant un suivi par le dosage des peptides collagéniques.

5.2 PERSPECTIVES

5.2.1 *Evaluation de l'intérêt de traitement anti-fibrotique chez des patients asymptomatiques à haut risque de développer une insuffisance cardiaque*

La classification ACC/AHA de 2005[6] considère également les patients hypertendus, obèses, diabétiques, porteurs d'athérosclérose non significative et présentant un syndrome métabolique comme étant des patients à haut risque de développer une insuffisance cardiaque.

Ces différents états favorisent la survenue d'un remodelage cardiaque et artériel dont le développement de fibrose myocardique et/ou péri-vasculaire est un élément fondamental[213]. En effet les patients hypertendus développent une hypertrophie réactionnelle à l'augmentation de la post charge. Cette hypertrophie comme explicité dans l'introduction se réalise aux dépends des cardiomyocytes mais également de la matrice extracellulaire avec une augmentation du dépôt de fibrose. Les patients hypertendus vont ainsi secondairement développer une hypertrophie ventriculaire gauche et une rigidité artérielle. Martos *et al.* a confirmé l'existence d'une augmentation de la fibrose myocardique chez des patients hypertendus asymptomatiques présentant une dysfonction diastolique. Cette fibrose est plus intense encore chez les sujets symptomatiques[214]. Plusieurs études animales[215,216] et humaines[217–219] ont confirmé l'intérêt des antagonistes du système rénine angiotensine et plus particulièrement des antagonistes des récepteurs aux minéralocorticoïdes dans les modèles d'animaux hypertendus par une action anti-fibrotique indépendamment de la baisse de pression artérielle.

Notre équipe a déjà mis en évidence la présence d'un turnover intense de la matrice extracellulaire chez les patients obèses sans autre facteur de risque cardiovasculaire[220]. Dans cette population nous avions montré l'existence d'une association positive entre

les concentrations en PIIINP et le ratio E/A. Pour la première fois il est mis en évidence par notre travail que les peptides collagéniques (PIIINP) sont associés à l'existence d'une dysfonction diastolique du ventricule gauche chez des patients asymptomatiques présentant comme seul facteur de risque cardiovasculaire une obésité abdominale.
Enfin il existe une augmentation de la fibrose myocardique (PINP) chez les patients atteints d'hyperaldostéronisme primaire régressant après traitement par antagonistes des récepteurs aux minéralocorticoïdes[221]. Les mêmes constats ont été réalisés chez des rats sur-exprimant les hormones du système rénine angiotensine[222].

Une des interrogations actuelles est donc de savoir s'il serait judicieux de traiter des patients asymptomatiques non hypertendus atteints d'obésité ou d'obésité abdominale par des anti-fibrotiques comme les antagonistes des récepteurs aux minéralocorticoïdes afin de prévenir leur possible évolution vers la dysfonction diastolique et l'insuffisance cardiaque. Des études de prévention primaire devront être menées en ce sens comme cela a pu être démontré concernant l'hypertension artérielle[223].

5.2.2 *Evaluation de l'intérêt de traitement anti-fibrotique chez des patients présentant une insuffisance cardiaque à fonction systolique préservée*

De nombreuses études[42,43,206] ont montré l'efficacité et la sécurité d'utilisation des antagonistes des récepteurs aux minéralocorticoïdes (spironolactone et éplérénone) chez des patients présentant une insuffisance cardiaque à fonction systolique ventriculaire gauche altérée sans lien avec le niveau de gravité. Ces études cliniques internationales ont permis à cette classe thérapeutique d'être recommandée en classe I, niveau de preuve A[5].

L'insuffisance cardiaque à fonction systolique préservée est le prochain défi pour les chercheurs et les cliniciens spécialistes de l'insuffisance cardiaque. En effet son

incidence et sa prévalence ne cessent d'augmenter. La prévalence de l'insuffisance cardiaque à fonction systolique préservée augmente plus rapidement que celle à fonction altérée ; alors qu'aucune amélioration du pronostic n'a été retrouvée[224]. Elle touche notamment les populations âgées qui constituent la grande majorité des patients pris en charge en hospitalisation. Malheureusement les mécanismes physiopathologiques ne sont pas encore totalement élucidés et donc les possibilités thérapeutiques encore limitées[225]. Les dernières recommandations ou articles dans le domaine incitent uniquement à la prise en charge des facteurs de risque, tels que l'hypertension artérielle, comme seuls traitements de l'insuffisance cardiaque à fonction systolique préservée[5,226].

La physiopathologie admise à l'heure actuelle est celle d'une rigidité myocardique due à une atteinte de la matrice extracellulaire et des cardiomyocytes[226]. Il existe une augmentation du dépôt de fibrose par augmentation de la production ou par une diminution de la dégradation de cette fibrose[227,228]. Plusieurs études ont mis en évidence que le PIIINP pouvait être un marqueur précoce du risque d'évolution vers l'insuffisance cardiaque à fonction systolique préservée mais également un marqueur de survenue d'évènements cardiovasculaires[185,229]. De plus les antagonistes des récepteurs aux minéralocorticoïdes ont montré leur intérêt sur une diminution de la fibrose myocardique chez ces patients[214,230].

Du fait de ces constatations plusieurs études ont essayé de valider l'intérêt en terme de morbi-mortalité des différents antagonistes du système rénine-angiotensine-aldostérone dans cette pathologie[227,231–233], alors que les études, utilisant les IEC ou les ARA II, se sont avérées négatives[231–233]. Des antagonistes des récepteurs aux minéralocorticoïdes ont montré un bénéfice sur des paramètres de dysfonction diastolique mais également sur des « surrogate endpoints » tels que les peptides collagéniques[234], la masse ventriculaire gauche, le NT-ProBNP[235] mais sans amélioration sur la qualité de vie, la classe NYHA ou la morbi-mortalité.

L'étude TOPCAT[236] devrait permettre de définir l'intérêt éventuel des antagonistes des récepteurs aux minéralocorticoïdes dans cette population. Cette étude, randomisée,

menée en double aveugle évalue l'intérêt du traitement par spironolactone chez des patients symptomatiques d'insuffisance cardiaque avec une fraction d'éjection du ventricule gauche conservée (FEVG ≥45%) ayant été hospitalisés dans l'année pour une décompensation d'insuffisance cardiaque ou avec une élévation des peptides natriurétiques sanguins (BNP ≥ 100pg/ml ou NT-ProBNP≥360 pg/ml). Le critère de jugement principal est composite : survenue de décès cardiovasculaire, ou d'hospitalisations pour insuffisance cardiaque ou d'arrêt cardiaque avorté.

5.2.3 *Evaluation de l'intérêt de traitement anti-fibrotique chez l'ensemble des patients présentant un syndrome coronarien aigu*

Les patients à plus haut risque de morbi-mortalité et de remodelage cardiaque en post syndrome coronarien aigu bénéficient de l'utilisation d'un traitement anti-fibrotique par éplérénone[43]. Il s'agit des patients présentant une dysfonction ventriculaire gauche post-infarctus (FEVG<40%) et des signes immédiat d'IC.

De plus, notre équipe a déjà mis en évidence la présence d'un dépôt intense de fibrose en post-infarctus immédiat avec des signes d'insuffisance cardiaque, notamment de PINP et de PIIINP 1 mois après l'infarctus[204]. Enfin les patients traités par éplérénone présentent une diminution plus importante des concentrations de peptides collagéniques (PINP, PIIINP) en comparaison aux patients traités par placebo.

Il est donc admis que les patients les plus graves sont le plus améliorés par l'éplérénone en post-infarctus du myocarde. Nous avons montré dans l'étude REVE-2 qu'y compris chez des patients moins sévèrement atteints (meilleure fonction ventriculaire gauche initiale, moins d'insuffisance cardiaque à la prise en charge) il existe également un dépôt de fibrose et que le ratio PIIINP / ICTP est associé au remodelage à 1 an et à la survie et aux hospitalisations pour IC à 3 ans.

Il est important de noter que plus l'aldostéronémie est élevée en post-infarctus immédiat plus la survie est mauvaise[237]. Il semblerait donc licite d'envisager de traiter l'ensemble des patients ayant présenté un syndrome coronarien aigu par des antagonistes des récepteurs aux minéralocorticoïdes afin de limiter leur remodelage ventriculaire gauche délétère et leur morbi-mortalité.

Des études sont déjà en cours[238]. Les résultats de l'étude Reminder viennent d'être présentés au congrès de l'American College of Cardiology par le Pr Montalecot. L'objectif de Reminder était d'évaluer le bénéfice de l'ajout d'éplérénone dans les 24 premières heures chez des patients pris en charge pour syndrome coronarien avec sus décalage du segment ST sur un critère composite (décès cardiovasculaires, hospitalisations pour IC ou allongement de l'hospitalisation initiale, troubles du rythme ventriculaires graves, FEVG ≤ 40% 1 mois après et augmentation du NT-ProBNP 1 mois après). En associant aux thérapeutiques habituelles (IEC, bêta-bloquants, anti-agrégants plaquettaires et statines) l'éplérénone était délivrée initialement à 25mg/jour puis augmentée à 50mg/jour (88.6% des patients recevaient en fin d'étude 50 mg/jour d'éplérénone). L'éplérénone a permis une diminution de 42% du critère primaire composite [HR(95%CI) = 0.581 (0.449-0.753), p<0.0001]. Cette diminution est principalement due à la non augmentation du BNP à 1 mois chez les patients traités par éplérénone. En effet, aucune différence significative n'a pu être mise en évidence pour les autres paramètres composant le critère primaire composite. Il n'y pas par contre pas eu de sur risque iatrogénique alors que l'éplérénone était donné sans prendre en compte l'état de la fonction rénale (les patients connus avec une eGFR<30ml/mn/1.73m^2 n'était tout de même pas inclus).

Il sera donc intéressant d'attendre les résultats de l'étude Albatross[238] (intérêt d'un traitement par soludactone à la phase aiguë des patients pris en charge pour un syndrome coronarien aigu avec sus-décalage du segment ST ou à haut risque sans sus-décalage sans signe d'insuffisance cardiaque) pour envisager l'ajout systématique des antagonistes des récepteurs aux minéralocorticoïdes chez tous les patients pris en charge pour syndrome coronarien aigu.

5.3 PERSPECTIVES DANS D'AUTRES POPULATIONS

L'intérêt des peptides collagéniques va être étudié dans d'autres populations grâce à des études en cours.

5.3.1 *Etude R2C2 II*

Afin de mieux appréhender les mécanismes de transition de l'obésité abdominale vers l'insuffisance cardiaque, nous nous proposons dans une nouvelle étude de convoquer à nouveau 3 à 5 ans après le phénotypage initial les patients inclus initialement (*cf.* R2C2 study). A la différence de notre première étude, uniquement transversale, nous allons pouvoir par cette étude longitudinale mieux étudier les mécanismes physiopathologiques liant l'obésité abdominale à l'insuffisance cardiaque. Les sujets vont bénéficier d'un phénotypage plus complet avec l'évaluation de la pression artérielle par MAPA, des pathologies respiratoires (dépistage des syndromes d'apnée du sommeil) fréquentes chez les obèses ainsi qu'une étude exhaustive du système rénine angiotensine complétée par un recueil urinaire des 24 heures. Bien entendu l'étude de la fibrose par biomarqueurs sera réalisée.

L'imagerie « gold standard » pour évaluer le remodelage ventriculaire gauche est dorénavant l'imagerie par résonnance magnétique. Celle-ci peut par des séquences particulières et complexes évaluer le degré d'infiltration de fibrose intra-myocardique. Mais ces résultats ne sont pas encore suffisamment robustes. Un PHRC national est en cours avec pour objectif de corréler les concentrations des peptides collagéniques à l'infiltrat fibrotique IRM dans les cardiomyopathies dilatées (Pr A Jacquier, Marseille).

Ceci pourrait nous permettre de conforter nos premières hypothèses émises après l'étude transversale : dysfonction diastolique, remodelage cardiaque délétère, rôle de la fibrose. Les premiers sujets ont déjà bénéficié de leur nouveau phénotypage dans le cadre d'un PHRC inter-régional (R2C2 II).

5.3.2 *HF80 pilot study*

L'incidence de l'IC ne cesse d'augmenter et notamment dans les populations âgées et très âgées[11]. Dans l'étude EPICA la prévalence après 80 ans est de 16,14%[239]. Les essais thérapeutiques ont montré que l'utilisation d'un traitement médical comprenant des inhibiteurs de l'enzyme de conversion, des bêta bloquants, des antagonistes des récepteurs aux minéralocorticoïdes, de l'ivabradine, ainsi qu'une thérapie par resynchronisation cardiaque, a permis une amélioration de la qualité de vie, une diminution de la mortalité, ainsi qu'une diminution du nombre de ré hospitalisations.
Malgré un pronostic sombre, les études observationnelles et les registres montrent une sous-prescription des traitements recommandés notamment les inhibiteurs de l'enzyme de conversion et les bêta bloquants chez les plus de 80 ans[240,241]. Mais les recommandations[5] se basent sur des essais cliniques incluant des patients dont la moyenne d'âge est de 65 à 70 ans. Aucun essai spécifique n'a étudié le bénéfice d'une prise en charge optimale après 80 ans.

Pour cette raison nous avons débuté fin 2011 une étude monocentrique au CHU de Clermont-Ferrand ayant pour objectif d'évaluer l'intérêt sur la qualité de vie à 6 mois, de l'optimisation du traitement de l'IC selon les recommandations chez les patients insuffisants cardiaques à fonction systolique altérée de plus de 80 ans (HF80 pilot study, NCT01437371, cf. Annexe 1)[242]. Une sérothèque a été créée. Celle-ci nous permettra notamment d'étudier l'importance de la fibrose chez ces patients et si un traitement optimal permet une diminution de celle-ci ou au contraire si la longue évolution de la pathologie empêche tout remodelage positif et impact sur la fibrose.

5.3.3 *Etude PREFAC-CRT*

La resynchronisation cardiaque électrique (CRT) est une thérapeutique validée de l'insuffisance cardiaque chez des patients présentant une dysfonction systolique sévère du ventricule gauche. Malheureusement 20 à 40% des patients implantés selon les recommandations ne bénéficient pas d'une amélioration de leur état[243]. La sélection des patients éligibles à la resynchronisation se fait selon les recommandations de la société européenne de cardiologie mais la détection en amont des patients non répondeurs reste imparfaite[244].

Nous avons donc initié une étude multicentrique (CHU Clermont-Ferrand, IHU Bordeaux, CHU Nancy et Clinique Pasteur Toulouse) dont l'objectif principal est d'identifier des paramètres prédictifs (clinique, biologique, échocardiographique, scintigraphique et IRM) d'une réponse positive à la resynchronisation cardiaque électrique. Cette approche, pour la première fois multimodale, nous permettra de proposer un score prédictif de réponse à la resynchronisation cardiaque et d'appréhender des pistes physiopathologiques.

Une sérothèque a également été créée dans cette population. L'intérêt de celle-ci est encore son implication multimodale avec notamment une évaluation de la fibrose myocardique par les peptides collagéniques mais une approche protéomique est également prévue. En effet il a déjà été montré qu'isolément les peptides collagéniques ne permettent pas de prédire une réponse à la resynchronisation et que leurs concentrations n'évoluent pas après resynchronisation[245].

Les inclusions ont débuté depuis le mois de mars 2013. 300 patients seront inclus.

5.4 LIMITES

Ce travail a permis d'appréhender de façon globale l'intérêt des peptides collagéniques aux différents stades de l'évolution de l'insuffisance cardiaque. Malgré cela certaines limites sont à signaler :

1/ Le design transversal et non longitudinal de l'étude chez les patients présentant une obésité abdominale (R2C2 study). C'est pour cette raison que les patients ont été convoqués à nouveau cinq années plus tard pour bénéficier d'un suivi longitudinal et ainsi évaluer plus clairement les mécanismes physiopathologiques de transition de l'obésité abdominale vers l'insuffisance cardiaque. Ceci nous permettra de potentiellement valider l'association de la fibrose myocardique avec la dysfonction diastolique, préalable nécessaire avant toute étude interventionnelle. Ces études interventionnelles pourront évaluer l'intérêt d'une adaptation thérapeutique anti-fibrotique (antagonistes des récepteurs aux minéralocorticoïdes par exemple) en fonction des taux de peptides collagéniques. Nous pourrons alors contrôler l'évolution de leurs concentrations et de leur éventuelle corrélation avec les évènements cardiovasculaires.

2/ La spécificité myocardique des peptides collagéniques n'est pas totale (cf. chapitre 2) mais des corrélations ont été réalisées[184] entre les concentrations de peptides collagéniques sanguins et la fibrose myocardique. Ces études permettent de retenir les peptides collagéniques comme des marqueurs fiables de la fibrose myocardique.

3/ Les études R2C2 et REVE-2 ont toutes les deux permis de mettre en évidence des éléments nouveaux. Afin de rendre ces éléments plus robustes il est nécessaire de confirmer ces données par des études de reproductibilité.

4/ Enfin, nous n'avons malheureusement pas pu vérifier l'impact sur la fibrose de l'éplérénone dans une population moyennement symptomatique grâce à une sous-étude

d'EMPHASIS-HF. Celle-ci aurait pu permettre de confirmer l'impact des traitements anti-fibrotiques dans des populations moins sévères que RALES et EPHESUS.

Il est tout de même important de noter que ces différents travaux ont été menés dans des populations très sélectionnées (obésité abdominale sans autre facteur de risque, premier infarctus du myocarde antérieur) avec une évaluation cardiovasculaire extrêmement précise par des méthodes robustes (lecture centralisée des échocardiographies dans REVE-2, IRM myocardique dans R2C2, critères durs d'évènements cardiovasculaires dans EMPHASIS-HF) conférant à ces résultats un intérêt certain.

6 CONCLUSION

Ce travail a permis de mettre en évidence la place centrale de la fibrose dans l'évolution de l'insuffisance cardiaque du stade asymptomatique aux stades les plus sévères par l'analyse des peptides collagéniques sanguins.

Nous montrons, chez des sujets asymptomatiques porteurs d'une obésité abdominale, la présence d'un remodelage ventriculaire gauche (augmentation de la masse ventriculaire gauche), et une proportion importante de sujets atteints d'une dysfonction diastolique associée aux peptides collagéniques.

Dans un deuxième temps l'analyse d'une population de patients ayant présenté un infarctus antérieur du myocarde a permis de valider l'intérêt pronostic des peptides collagéniques à 3 ans mais également de montrer qu'ils apportent un bénéfice pour identifier les patients à haut risque de remodelage qui seraient insuffisamment identifiés par des paramètres habituels.

Enfin l'étape thérapeutique a pu être validée par une analyse en sous-groupes d'EMPHASIS-HF montrant la sécurité et le bénéfice d'utilisation des antagonistes des récepteurs aux minéralocorticoïde chez des patients avec de nombreuses co morbidités et à haut risque de remodelage.

Ce travail doit conduire à la validation dans d'autres populations, du rôle prépondérant de la fibrose mais surtout du bénéfice thérapeutique des classes anti-fibrotiques dans l'insuffisance cardiaque.

7 RÉFÉRENCES BIBLIOGRAPHIQUES

1. Denolin H, Kuhn H, Krayenbuehl HP, Loogen F, Reale A. The definition of heart failure. *Eur. Heart J.* 1983; 4:445–448.

2. Krum H, Abraham WT. Heart failure. *Lancet*. 2009; 373:941–955.

3. Fisher JD. New York Heart Association Classification. *Arch. Intern. Med.* 1972; 129:836.

4. Bennett JA, Riegel B, Bittner V, Nichols J. Validity and reliability of the NYHA classes for measuring research outcomes in patients with cardiac disease. *Heart & Lung: The Journal of Acute and Critical Care*. 2002; 31:262–270.

5. McMurray JJV, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur. J. Heart Fail.* 2012; 14:803–869.

6. Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *J. Am. Coll. Cardiol*. 2005; 46:e1–82.

7. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community-based population. *JAMA*. 2004; 292:344–350.

8. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KKL, Murabito JM, Vasan RS. Long-term trends in the incidence of and survival with heart failure. *N. Engl. J. Med.* 2002; 347:1397–1402.

9. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart*. 2007; 93:1137–1146.

10. Saudubray T, Saudubray C, Viboud C, Jondeau G, Valleron A-J, Flahault A, Hanslik T. [Prevalence and management of heart failure in France: national study among general practitioners of the Sentinelles network]. *Rev Med Interne*. 2005; 26:845–850.

11. Delahaye F, de Gevigney G, Gaillard S, Cheneau E. [Epidemiology and economic impact of heart failure in France]. *Arch Mal Coeur Vaiss*. 1998; 91:1307–1314.

12. Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: the Framingham Study. *J. Am. Coll. Cardiol*. 1993; 22:6A–13A.

13. Kannel WB, Belanger AJ. Epidemiology of heart failure. *Am. Heart J.* 1991; 121:951–957.

14. Logeart D, Isnard R, Resche-Rigon M, Seronde M-F, de Groote P, Jondeau G, Galinier M, Mulak G, Donal E, Delahaye F, Juilliere Y, Damy T, Jourdain P, Bauer F, Eicher J-C, Neuder Y, Trochu J-N, Heart Failure of the French Society of Cardiology. Current aspects of the spectrum of acute heart failure syndromes in a real-life setting: the OFICA study. *Eur. J. Heart Fail.* 2013; 15:465–476.

15. Laribi S, Aouba A, Nikolaou M, Lassus J, Cohen-Solal A, Plaisance P, Pavillon G, Jois P, Fonarow GC, Jougla E, Mebazaa A, GREAT network. Trends in death attributed to heart failure over the past two decades in Europe. *Eur. J. Heart Fail.* 2012; 14:234–239.

16. Grossman W, McLaurin LP, Stefadouros MA. Left ventricular stiffness associated with chronic pressure and volume overloads in man. *Circ. Res.* 1974; 35:793–800.

17. Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. *Circulation*. 2000; 102:IV14–23.

18. Mitchell GF, Lamas GA, Vaughan DE, Pfeffer MA. Left ventricular remodeling in the year after first anterior myocardial infarction: a quantitative analysis of contractile segment lengths and ventricular shape. *J. Am. Coll. Cardiol.* 1992; 19:1136–1144.

19. Abrahamsson P, Dobson J, Granger CB, McMurray JJV, Michelson EL, Pfeffer M, Pocock S, Solomon SD, Yusuf S, Swedberg K, CHARM Investigators. Impact of hospitalization for acute coronary events on subsequent mortality in patients with chronic heart failure. *Eur. Heart J.* 2009; 30:338–345.

20. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN. The neurohumoral axis in congestive heart failure. *Ann. Intern. Med.* 1984; 101:370–377.

21. Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. *N. Engl. J. Med.* 1990; 323:236–241.

22. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N. Engl. J. Med.* 1984; 311:819–823.

23. Güder G, Bauersachs J, Frantz S, Weismann D, Allolio B, Ertl G, Angermann CE, Störk S. Complementary and incremental mortality risk prediction by cortisol and aldosterone in chronic heart failure. *Circulation*. 2007; 115:1754–1761.

24. Narula J, Haider N, Virmani R, DiSalvo TG, Kolodgie FD, Hajjar RJ, Schmidt U, Semigran MJ, Dec GW, Khaw BA. Apoptosis in myocytes in end-stage heart failure. *N. Engl. J. Med.* 1996; 335:1182–1189.

25. Olivetti G, Abbi R, Quaini F, Kajstura J, Cheng W, Nitahara JA, Quaini E, Di Loreto C, Beltrami CA, Krajewski S, Reed JC, Anversa P. Apoptosis in the failing human heart. *N. Engl. J. Med.* 1997; 336:1131–1141.

26. Pogwizd SM, Schlotthauer K, Li L, Yuan W, Bers DM. Arrhythmogenesis and contractile dysfunction in heart failure: Roles of sodium-calcium exchange, inward rectifier potassium current, and residual beta-adrenergic responsiveness. *Circ. Res.* 2001; 88:1159–1167.

27. MacLennan DH, Kranias EG. Phospholamban: a crucial regulator of cardiac contractility. *Nat. Rev. Mol. Cell Biol.* 2003; 4:566–577.

28. Rodriguez P, Kranias EG. Phospholamban: a key determinant of cardiac function and dysfunction. *Arch Mal Coeur Vaiss*. 2005; 98:1239–1243.

29. Bers DM. Macromolecular complexes regulating cardiac ryanodine receptor function. *J. Mol. Cell. Cardiol.* 2004; 37:417–429.

30. Rubart M, Zipes DP. Mechanisms of sudden cardiac death. *J. Clin. Invest.* 2005; 115:2305–2315.

31. McMurray JJV. Clinical practice. Systolic heart failure. *N. Engl. J. Med.* 2010; 362:228–238.

32. Shah AM, Mann DL. In search of new therapeutic targets and strategies for heart failure: recent advances in basic science. *Lancet*. 2011; 378:704–712.

33. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N. Engl. J. Med.* 1971; 285:1441–1446.

34. Jhund PS, Macintyre K, Simpson CR, Lewsey JD, Stewart S, Redpath A, Chalmers JWT, Capewell S, McMurray JJV. Long-term trends in first hospitalization for heart failure and subsequent survival between 1986 and 2003: a population study of 5.1 million people. *Circulation*. 2009; 119:515–523.

35. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N. Engl. J. Med*. 1987; 316:1429–1435.

36. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N. Engl. J. Med.* 1991; 325:293–302.

37. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. *JAMA.* 1995; 273:1450–1456.

38. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL. Effect of carvedilol on survival in severe chronic heart failure. *N. Engl. J. Med*. 2001; 344:1651–1658.

39. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999; 353:2001–2007.

40. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999; 353:9–13.

41. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Böhm M, Anker SD, Thompson SG, Poole-Wilson PA. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). *Eur. Heart J*. 2005; 26:215–225.

42. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med*. 1999; 341:709–717.

43. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N. Engl. J. Med*. 2003; 348:1309–1321.

44. Zannad F, McMurray JJV, Drexler H, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pitt B. Rationale and design of the Eplerenone in Mild Patients Hospitalization And SurvIval Study in Heart Failure (EMPHASIS-HF). *Eur. J. Heart Fail.* 2010; 12:617–622.

45. Bélanger-Ducharme F, Tremblay A. Prevalence of obesity in Canada. *Obes Rev*. 2005; 6:183–186.

46. Hu G, Qiao Q, Tuomilehto J, Eliasson M, Feskens EJM, Pyörälä K, DECODE Insulin Study Group. Plasma insulin and cardiovascular mortality in non-diabetic European men and women: a meta-analysis of data from eleven prospective studies. *Diabetologia*. 2004; 47:1245–1256.

47. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature*. 2001; 414:782–787.

48. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, Speizer FE, Manson JE. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. *Am. J. Epidemiol.* 1997; 145:614–619.

49. Holt RIG. International Diabetes Federation re-defines the metabolic syndrome. *Diabetes Obes Metab*. 2005; 7:618–620.

50. Pouliot MC, Després JP, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. *Am. J. Cardiol.* 1994; 73:460–468.

51. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willett WC, Manson JE. Abdominal adiposity and coronary heart disease in women. *JAMA*. 1998; 280:1843–1848.

52. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002; 287:356–359.

53. Dallongeville J, Cottel D, Ferrières J, Arveiler D, Bingham A, Ruidavets JB, Haas B, Ducimetière P, Amouyel P. Household income is associated with the risk of metabolic syndrome in a sex-specific manner. *Diabetes Care*. 2005; 28:409–415.

54. Gu D, Reynolds K, Wu X, Chen J, Duan X, Reynolds RF, Whelton PK, He J, InterASIA Collaborative Group. Prevalence of the metabolic syndrome and overweight among adults in China. *Lancet*. 2005; 365:1398–1405.

55. Ford ES. Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: a summary of the evidence. *Diabetes Care*. 2005; 28:1769–1778.

56. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002; 288:1723–1727.

57. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. 2010; 303:235–241.

58. Gutiérrez-Fisac JL, Guallar-Castillón P, León-Muñoz LM, Graciani A, Banegas JR, Rodríguez-Artalejo F. Prevalence of general and abdominal obesity in the adult population of Spain, 2008-2010: the ENRICA study. *Obes Rev*. 2012; 13:388–392.

59. Li C, Ford ES, McGuire LC, Mokdad AH. Increasing trends in waist circumference and abdominal obesity among US adults. *Obesity (Silver Spring)*. 2007; 15:216–224.

60. Walls HL, Stevenson CE, Mannan HR, Abdullah A, Reid CM, McNeil JJ, Peeters A. Comparing trends in BMI and waist circumference. *Obesity (Silver Spring)*. 2011; 19:216–219.

61. Reynolds K, Gu D, Whelton PK, Wu X, Duan X, Mo J, He J, InterASIA Collaborative Group. Prevalence and risk factors of overweight and obesity in China. *Obesity (Silver Spring)*. 2007; 15:10–18.

62. Macia E, Duboz P, Gueye L. Prevalence of obesity in Dakar. *Obes Rev*. 2010; 11:691–694.

63. Xi B, Liang Y, He T, Reilly KH, Hu Y, Wang Q, Yan Y, Mi J. Secular trends in the prevalence of general and abdominal obesity among Chinese adults, 1993-2009. *Obes Rev*. 2012; 13:287–296.

64. Wardle J, Boniface D. Changes in the distributions of body mass index and waist circumference in English adults, 1993/1994 to 2002/2003. *Int J Obes (Lond)*. 2008; 32:527–532.

65. Booth ML, Hunter C, Gore CJ, Bauman A, Owen N. The relationship between body mass index and waist circumference: implications for estimates of the population prevalence of overweight. *Int. J. Obes. Relat. Metab. Disord.* 2000; 24:1058–1061.

66. Mazumder PK, O'Neill BT, Roberts MW, Buchanan J, Yun UJ, Cooksey RC, Boudina S, Abel ED. Impaired cardiac efficiency and increased fatty acid oxidation in insulin-resistant ob/ob mouse hearts. *Diabetes*. 2004; 53:2366–2374.

67. Buchanan J, Mazumder PK, Hu P, Chakrabarti G, Roberts MW, Yun UJ, Cooksey RC, Litwin SE, Abel ED. Reduced cardiac efficiency and altered substrate metabolism precedes the onset of hyperglycemia and contractile dysfunction in two mouse models of insulin resistance and obesity. *Endocrinology*. 2005; 146:5341–5349.

68. Aizawa-Abe M, Ogawa Y, Masuzaki H, Ebihara K, Satoh N, Iwai H, Matsuoka N, Hayashi T, Hosoda K, Inoue G, Yoshimasa Y, Nakao K. Pathophysiological role of leptin in obesity-related hypertension. *J. Clin. Invest.* 2000; 105:1243–1252.

69. Masuzaki H, Yamamoto H, Kenyon CJ, Elmquist JK, Morton NM, Paterson JM, Shinyama H, Sharp MGF, Fleming S, Mullins JJ, Seckl JR, Flier JS. Transgenic amplification of glucocorticoid action in adipose tissue causes high blood pressure in mice. *J. Clin. Invest.* 2003; 112:83–90.

70. Finck BN, Lehman JJ, Leone TC, Welch MJ, Bennett MJ, Kovacs A, Han X, Gross RW, Kozak R, Lopaschuk GD, Kelly DP. The cardiac phenotype induced by PPARalpha overexpression mimics that caused by diabetes mellitus. *J. Clin. Invest.* 2002; 109:121–130.

71. Russell JC, Proctor SD. Small animal models of cardiovascular disease: tools for the study of the roles of metabolic syndrome, dyslipidemia, and atherosclerosis. *Cardiovasc. Pathol.* 2006; 15:318–330.

72. Carley AN, Severson DL. Fatty acid metabolism is enhanced in type 2 diabetic hearts. *Biochim. Biophys. Acta*. 2005; 1734:112–126.

73. Severson DL. Diabetic cardiomyopathy: recent evidence from mouse models of type 1 and type 2 diabetes. *Can. J. Physiol. Pharmacol.* 2004; 82:813–823.

74. Boudina S, Sena S, Theobald H, Sheng X, Wright JJ, Hu XX, Aziz S, Johnson JI, Bugger H, Zaha VG, Abel ED. Mitochondrial energetics in the heart in obesity-related diabetes: direct evidence for increased uncoupled respiration and activation of uncoupling proteins. *Diabetes*. 2007; 56:2457–2466.

75. Abel ED. Myocardial insulin resistance and cardiac complications of diabetes. *Curr. Drug Targets Immune Endocr. Metabol. Disord.* 2005; 5:219–226.

76. Després J-P. Inflammation and cardiovascular disease: is abdominal obesity the missing link? *Int. J. Obes. Relat. Metab. Disord.* 2003; 27 Suppl 3:S22–24.

77. Ingelsson E, Arnlöv J, Sundström J, Lind L. Inflammation, as measured by the erythrocyte sedimentation rate, is an independent predictor for the development of heart failure. *J. Am. Coll. Cardiol.* 2005; 45:1802–1806.

78. Barouch LA, Gao D, Chen L, Miller KL, Xu W, Phan AC, Kittleson MM, Minhas KM, Berkowitz DE, Wei C, Hare JM. Cardiac myocyte apoptosis is associated with increased DNA damage and decreased survival in murine models of obesity. *Circ. Res.* 2006; 98:119–124.

79. Engeli S, Negrel R, Sharma AM. Physiology and pathophysiology of the adipose tissue renin-angiotensin system. *Hypertension*. 2000; 35:1270–1277.

80. Engeli S, Böhnke J, Gorzelniak K, Janke J, Schling P, Bader M, Luft FC, Sharma AM. Weight loss and the renin-angiotensin-aldosterone system. *Hypertension*. 2005; 45:356–362.

81. van Harmelen V, Elizalde M, Ariapart P, Bergstedt-Lindqvist S, Reynisdottir S, Hoffstedt J, Lundkvist I, Bringman S, Arner P. The association of human adipose angiotensinogen gene expression with abdominal fat distribution in obesity. *Int. J. Obes. Relat. Metab. Disord*. 2000; 24:673–678.

82. Davy KP, Hall JE. Obesity and hypertension: two epidemics or one? *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2004; 286:R803–813.

83. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *J. Clin. Endocrinol. Metab.* 2004; 89:2548–2556.

84. Iacobellis G, Leonetti F, Singh N, M Sharma A. Relationship of epicardial adipose tissue with atrial dimensions and diastolic function in morbidly obese subjects. *Int. J. Cardiol.* 2007; 115:272–273.

85. Malavazos AE, Ermetici F, Coman C, Corsi MM, Morricone L, Ambrosi B. Influence of epicardial adipose tissue and adipocytokine levels on cardiac abnormalities in visceral obesity. *Int. J. Cardiol.* 2007; 121:132–134.

86. Fang X, Sweeney G. Mechanisms regulating energy metabolism by adiponectin in obesity and diabetes. *Biochem. Soc. Trans.* 2006; 34:798–801.

87. Yamauchi T, Kadowaki T. Physiological and pathophysiological roles of adiponectin and adiponectin receptors in the integrated regulation of metabolic and cardiovascular diseases. *Int J Obes (Lond).* 2008; 32 Suppl 7:S13–18.

88. Waki H, Yamauchi T, Kamon J, Kita S, Ito Y, Hada Y, Uchida S, Tsuchida A, Takekawa S, Kadowaki T. Generation of globular fragment of adiponectin by leukocyte elastase secreted by monocytic cell line THP-1. *Endocrinology*. 2005; 146:790–796.

89. Wang Y, Lam KSL, Chan L, Chan KW, Lam JBB, Lam MC, Hoo RCL, Mak WWN, Cooper GJS, Xu A. Post-translational modifications of the four conserved lysine residues within the collagenous domain of adiponectin are required for the formation of its high molecular weight oligomeric complex. *J. Biol. Chem.* 2006; 281:16391–16400.

90. Liu Y, Retnakaran R, Hanley A, Tungtrongchitr R, Shaw C, Sweeney G. Total and high molecular weight but not trimeric or hexameric forms of adiponectin correlate with markers of the metabolic syndrome and liver injury in Thai subjects. *J. Clin. Endocrinol. Metab.* 2007; 92:4313–4318.

91. Fang X, Palanivel R, Cresser J, Schram K, Ganguly R, Thong FSL, Tuinei J, Xu A, Abel ED, Sweeney G. An APPL1-AMPK signaling axis mediates beneficial metabolic effects of adiponectin in the heart. *Am. J. Physiol. Endocrinol. Metab.* 2010; 299:E721–729.

92. Palanivel R, Fang X, Park M, Eguchi M, Pallan S, De Girolamo S, Liu Y, Wang Y, Xu A, Sweeney G. Globular and full-length forms of adiponectin mediate specific changes in glucose and fatty acid uptake and metabolism in cardiomyocytes. *Cardiovasc. Res.* 2007; 75:148–157.

93. Abel ED, Litwin SE, Sweeney G. Cardiac remodeling in obesity. *Physiol. Rev.* 2008; 88:389–419.

94. Shetty S, Kusminski CM, Scherer PE. Adiponectin in health and disease: evaluation of adiponectin-targeted drug development strategies. *Trends Pharmacol. Sci.* 2009; 30:234–239.

95. Hui X, Lam KSL, Vanhoutte PM, Xu A. Adiponectin and cardiovascular health: an update. *Br. J. Pharmacol.* 2012; 165:574–590.

96. Liao Y, Takashima S, Maeda N, Ouchi N, Komamura K, Shimomura I, Hori M, Matsuzawa Y, Funahashi T, Kitakaze M. Exacerbation of heart failure in adiponectin-deficient mice due to impaired regulation of AMPK and glucose metabolism. *Cardiovasc. Res.* 2005; 67:705–713.

97. Konishi M, Haraguchi G, Ohigashi H, Ishihara T, Saito K, Nakano Y, Isobe M. Adiponectin protects against doxorubicin-induced cardiomyopathy by anti-apoptotic effects through AMPK up-regulation. *Cardiovasc. Res.* 2011; 89:309–319.

98. Park M, Youn B, Zheng X, Wu D, Xu A, Sweeney G. Globular adiponectin, acting via AdipoR1/APPL1, protects H9c2 cells from hypoxia/reoxygenation-induced apoptosis. *PLoS ONE*. 2011; 6:e19143.

99. Shibata R, Ouchi N, Ito M, Kihara S, Shiojima I, Pimentel DR, Kumada M, Sato K, Schiekofer S, Ohashi K, Funahashi T, Colucci WS, Walsh K. Adiponectin-mediated modulation of hypertrophic signals in the heart. *Nat. Med.* 2004; 10:1384–1389.

100. Shibata R, Sato K, Pimentel DR, Takemura Y, Kihara S, Ohashi K, Funahashi T, Ouchi N, Walsh K. Adiponectin protects against myocardial ischemia-reperfusion injury through AMPK- and COX-2-dependent mechanisms. *Nat. Med.* 2005; 11:1096–1103.

101. Ouchi N, Shibata R, Walsh K. Cardioprotection by adiponectin. *Trends Cardiovasc. Med.* 2006; 16:141–146.

102. Shibata R, Izumiya Y, Sato K, Papanicolaou K, Kihara S, Colucci WS, Sam F, Ouchi N, Walsh K. Adiponectin protects against the development of systolic dysfunction following myocardial infarction. *J. Mol. Cell. Cardiol.* 2007; 42:1065–1074.

103. Fujita K, Maeda N, Sonoda M, Ohashi K, Hibuse T, Nishizawa H, Nishida M, Hiuge A, Kurata A, Kihara S, Shimomura I, Funahashi T. Adiponectin protects against angiotensin II-induced cardiac fibrosis through activation of PPAR-alpha. *Arterioscler. Thromb. Vasc. Biol.* 2008; 28:863–870.

104. Hong SJ, Park CG, Seo HS, Oh DJ, Ro YM. Associations among plasma adiponectin, hypertension, left ventricular diastolic function and left ventricular mass index. *Blood Press.* 2004; 13:236–242.

105. Wang C, Li L, Zhang Z-G, Fan D, Zhu Y, Wu L-L. Globular adiponectin inhibits angiotensin II-induced nuclear factor kappaB activation through AMP-activated protein kinase in cardiac hypertrophy. *J. Cell. Physiol.* 2010; 222:149–155.

106. Amin RH, Mathews ST, Alli A, Leff T. Endogenously produced adiponectin protects cardiomyocytes from hypertrophy by a PPARgamma-dependent autocrine mechanism. *Am. J. Physiol. Heart Circ. Physiol.* 2010; 299:H690–698.

107. Essick EE, Ouchi N, Wilson RM, Ohashi K, Ghobrial J, Shibata R, Pimentel DR, Sam F. Adiponectin mediates cardioprotection in oxidative stress-induced cardiac myocyte remodeling. *Am. J. Physiol. Heart Circ. Physiol.* 2011; 301:H984–993.

108. Sweeney G. Cardiovascular effects of leptin. *Nat Rev Cardiol*. 2010; 7:22–29.

109. Ahima RS, Flier JS. Leptin. *Annu. Rev. Physiol.* 2000; 62:413–437.

110. Martin SS, Qasim A, Reilly MP. Leptin resistance: a possible interface of inflammation and metabolism in obesity-related cardiovascular disease. *J. Am. Coll. Cardiol*. 2008; 52:1201–1210.

111. Enriori PJ, Evans AE, Sinnayah P, Cowley MA. Leptin resistance and obesity. *Obesity (Silver Spring)*. 2006; 14 Suppl 5:254S–258S.

112. Koh KK, Park SM, Quon MJ. Leptin and cardiovascular disease: response to therapeutic interventions. *Circulation*. 2008; 117:3238–3249.

113. Sharma V, Mustafa S, Patel N, Wambolt R, Allard MF, McNeill JH. Stimulation of cardiac fatty acid oxidation by leptin is mediated by a nitric oxide-p38 MAPK-dependent mechanism. *Eur. J. Pharmacol.* 2009; 617:113–117.

114. Atkinson LL, Fischer MA, Lopaschuk GD. Leptin activates cardiac fatty acid oxidation independent of changes in the AMP-activated protein kinase-acetyl-CoA carboxylase-malonyl-CoA axis. *J. Biol. Chem.* 2002; 277:29424–29430.

115. Palanivel R, Eguchi M, Shuralyova I, Coe I, Sweeney G. Distinct effects of short- and long-term leptin treatment on glucose and fatty acid uptake and metabolism in HL-1 cardiomyocytes. *Metab. Clin. Exp.* 2006; 55:1067–1075.

116. McGaffin KR, Zou B, McTiernan CF, O'Donnell CP. Leptin attenuates cardiac apoptosis after chronic ischaemic injury. *Cardiovasc. Res.* 2009; 83:313–324.

117. Shin E-J, Schram K, Zheng X-L, Sweeney G. Leptin attenuates hypoxia/reoxygenation-induced activation of the intrinsic pathway of apoptosis in rat H9c2 cells. *J. Cell. Physiol.* 2009; 221:490–497.

118. Eguchi M, Liu Y, Shin E-J, Sweeney G. Leptin protects H9c2 rat cardiomyocytes from H2O2-induced apoptosis. *FEBS J.* 2008; 275:3136–3144.

119. Rajapurohitam V, Javadov S, Purdham DM, Kirshenbaum LA, Karmazyn M. An autocrine role for leptin in mediating the cardiomyocyte hypertrophic effects of angiotensin II and endothelin-1. *J. Mol. Cell. Cardiol.* 2006; 41:265–274.

120. Abe Y, Ono K, Kawamura T, Wada H, Kita T, Shimatsu A, Hasegawa K. Leptin induces elongation of cardiac myocytes and causes eccentric left ventricular dilatation with compensation. *Am. J. Physiol. Heart Circ. Physiol.* 2007; 292:H2387–2396.

121. Zeidan A, Javadov S, Karmazyn M. Essential role of Rho/ROCK-dependent processes and actin dynamics in mediating leptin-induced hypertrophy in rat neonatal ventricular myocytes. *Cardiovasc. Res.* 2006; 72:101–111.

122. Barouch LA, Berkowitz DE, Harrison RW, O'Donnell CP, Hare JM. Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice. *Circulation*. 2003; 108:754–759.

123. Zhou YT, Grayburn P, Karim A, Shimabukuro M, Higa M, Baetens D, Orci L, Unger RH. Lipotoxic heart disease in obese rats: implications for human obesity. *Proc. Natl. Acad. Sci. U.S.A.* 2000; 97:1784–1789.

124. Zaman AK, Fujii S, Sawa H, Goto D, Ishimori N, Watano K, Kaneko T, Furumoto T, Sugawara T, Sakuma I, Kitabatake A, Sobel BE. Angiotensin-converting enzyme inhibition attenuates hypofibrinolysis and reduces cardiac perivascular fibrosis in genetically obese diabetic mice. *Circulation*. 2001; 103:3123–3128.

125. Zaman AKMT, Fujii S, Goto D, Furumoto T, Mishima T, Nakai Y, Dong J, Imagawa S, Sobel BE, Kitabatake A. Salutary effects of attenuation of angiotensin II on coronary perivascular fibrosis associated with insulin resistance and obesity. *J. Mol. Cell. Cardiol.* 2004; 37:525–535.

126. Madani S, De Girolamo S, Muñoz DM, Li R-K, Sweeney G. Direct effects of leptin on size and extracellular matrix components of human pediatric ventricular myocytes. *Cardiovasc. Res.* 2006; 69:716–725.

127. Purdham DM, Rajapurohitam V, Zeidan A, Huang C, Gross GJ, Karmazyn M. A neutralizing leptin receptor antibody mitigates hypertrophy and hemodynamic dysfunction in the postinfarcted rat heart. *Am. J. Physiol. Heart Circ. Physiol.* 2008; 295:H441–446.

128. Parish RC, Evans JD. Inflammation in chronic heart failure. *Ann Pharmacother*. 2008; 42:1002–1016.

129. Yndestad A, Damås JK, Øie E, Ueland T, Gullestad L, Aukrust P. Role of inflammation in the progression of heart failure. *Curr Cardiol Rep*. 2007; 9:236–241.

130. Yndestad A, Damås JK, Oie E, Ueland T, Gullestad L, Aukrust P. Systemic inflammation in heart failure--the whys and wherefores. *Heart Fail Rev*. 2006; 11:83–92.

131. Haynes WG. Role of leptin in obesity-related hypertension. *Exp. Physiol.* 2005; 90:683–688.

132. Rahmouni K, Morgan DA, Morgan GM, Mark AL, Haynes WG. Role of selective leptin resistance in diet-induced obesity hypertension. *Diabetes*. 2005; 54:2012–2018.

133. Beltowski J. Leptin and atherosclerosis. *Atherosclerosis*. 2006; 189:47–60.

134. Korda M, Kubant R, Patton S, Malinski T. Leptin-induced endothelial dysfunction in obesity. *Am. J. Physiol. Heart Circ. Physiol.* 2008; 295:H1514–1521.

135. Nakata M, Yada T, Soejima N, Maruyama I. Leptin promotes aggregation of human platelets via the long form of its receptor. *Diabetes*. 1999; 48:426–429.

136. Dellas C, Schäfer K, Rohm I, Lankeit M, Ellrott T, Faustin V, Riggert J, Hasenfuss G, Konstantinides S. Absence of leptin resistance in platelets from morbidly obese individuals may contribute to the increased thrombosis risk in obesity. *Thromb. Haemost.* 2008; 100:1123–1129.

137. Bodary PF, Westrick RJ, Wickenheiser KJ, Shen Y, Eitzman DT. Effect of leptin on arterial thrombosis following vascular injury in mice. *JAMA*. 2002; 287:1706–1709.

138. Elbatarny HS, Maurice DH. Leptin-mediated activation of human platelets: involvement of a leptin receptor and phosphodiesterase 3A-containing cellular signaling complex. *Am. J. Physiol. Endocrinol. Metab.* 2005; 289:E695–702.

139. Kenchaiah S, Evans JC, Levy D, Wilson PWF, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N. Engl. J. Med*. 2002; 347:305–313.

140. Prospective Studies Collaboration, Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, Halsey J, Qizilbash N, Collins R, Peto R. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet*. 2009; 373:1083–1096.

141. McCullough PA, Philbin EF, Spertus JA, Kaatz S, Sandberg KR, Weaver WD, Resource Utilization Among Congestive Heart Failure (REACH) Study. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. *J. Am. Coll. Cardiol.* 2002; 39:60–69.

142. Lavie CJ, Osman AF, Milani RV, Mehra MR. Body composition and prognosis in chronic systolic heart failure: the obesity paradox. *Am. J. Cardiol.* 2003; 91:891–894.

143. Khan MF, Movahed MR. Obesity cardiomyopathy and systolic function: obesity is not independently associated with dilated cardiomyopathy. *Heart Fail Rev*. 2013; 18:207–217.

144. Owan T, Litwin SE. Is there a cardiomyopathy of obesity? *Curr Heart Fail Rep*. 2007; 4:221–228.

145. Hu G, Jousilahti P, Antikainen R, Katzmarzyk PT, Tuomilehto J. Joint Effects of Physical Activity, Body Mass Index, Waist Circumference, and Waist-to-Hip Ratio on the Risk of Heart Failure. *Circulation*. 2010; 121:237 –244.

146. Petursson H, Sigurdsson JA, Bengtsson C, Nilsen TIL, Getz L. Body configuration as a predictor of mortality: comparison of five anthropometric measures in a 12 year follow-up of the Norwegian HUNT 2 study. *PLoS ONE*. 2011; 6:e26621.

147. Boggs DA, Rosenberg L, Cozier YC, Wise LA, Coogan PF, Ruiz-Narvaez EA, Palmer JR. General and abdominal obesity and risk of death among black women. *N. Engl. J. Med.* 2011; 365:901–908.

148. Coutinho T, Goel K, Corrêa de Sá D, Kragelund C, Kanaya AM, Zeller M, Park J-S, Kober L, Torp-Pedersen C, Cottin Y, Lorgis L, Lee S-H, Kim Y-J, Thomas R, Roger VL, Somers VK, Lopez-Jimenez F. Central obesity and survival in subjects with coronary artery disease: a systematic review of the literature and collaborative analysis with individual subject data. *J. Am. Coll. Cardiol.* 2011; 57:1877–1886.

149. Coutinho T, Goel K, Corrêa de Sá D, Carter RE, Hodge DO, Kragelund C, Kanaya AM, Zeller M, Park JS, Kober L, Torp-Pedersen C, Cottin Y, Lorgis L, Lee S-H, Kim Y-J, Thomas R, Roger VL, Somers VK, Lopez-Jimenez F. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of "normal weight central obesity."*J. Am. Coll. Cardiol.* 2013; 61:553–560.

150. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH. Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults. *Hypertension*. 1994; 23:600–606.

151. de Simone G, Kizer JR, Chinali M, Roman MJ, Bella JN, Best LG, Lee ET, Devereux RB, Strong Heart Study Investigators. Normalization for body size and population-attributable risk of left ventricular hypertrophy: the Strong Heart Study. *Am. J. Hypertens.* 2005; 18:191–196.

152. Alexander JK. The cardiomyopathy of obesity. *Prog Cardiovasc Dis*. 1985; 27:325–334.

153. Alpert MA, Terry BE, Kelly DL. Effect of weight loss on cardiac chamber size, wall thickness and left ventricular function in morbid obesity. *Am. J. Cardiol.* 1985; 55:783–786.

154. Alpert MA, Terry BE, Mulekar M, Cohen MV, Massey CV, Fan TM, Panayiotou H, Mukerji V. Cardiac morphology and left ventricular function in normotensive morbidly obese patients with and without congestive heart failure, and effect of weight loss. *Am. J. Cardiol.* 1997; 80:736–740.

155. Wang TJ, Parise H, Levy D, D'Agostino RB Sr, Wolf PA, Vasan RS, Benjamin EJ. Obesity and the risk of new-onset atrial fibrillation. *JAMA*. 2004; 292:2471–2477.

156. Cittadini A, Mantzoros CS, Hampton TG, Travers KE, Katz SE, Morgan JP, Flier JS, Douglas PS. Cardiovascular abnormalities in transgenic mice with reduced brown fat: an animal model of human obesity. *Circulation*. 1999; 100:2177–2183.

157. Toblli JE, Cao G, DeRosa G, Forcada P. Reduced cardiac expression of plasminogen activator inhibitor 1 and transforming growth factor beta1 in obese Zucker rats by perindopril. *Heart*. 2005; 91:80–86.

158. Brilla CG, Funck RC, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation*. 2000; 102:1388–1393.

159. Silvestre JS, Heymes C, Oubénaïssa A, Robert V, Aupetit-Faisant B, Carayon A, Swynghedauw B, Delcayre C. Activation of cardiac aldosterone production in rat myocardial infarction: effect of angiotensin II receptor blockade and role in cardiac fibrosis. *Circulation*. 1999; 99:2694–2701.

160. Diercks DB, Roe MT, Mulgund J, Pollack CV Jr, Kirk JD, Gibler WB, Ohman EM, Smith SC Jr, Boden WE, Peterson ED. The obesity paradox in non-ST-segment elevation acute coronary syndromes: results from the Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association Guidelines Quality Improvement Initiative. *Am. Heart J.* 2006; 152:140–148.

161. Habbu A, Lakkis NM, Dokainish H. The obesity paradox: fact or fiction? *Am. J. Cardiol.* 2006; 98:944–948.

162. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction, Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD, Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA, ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H, Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ, Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW, Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand J-P, Menasche P, Ravkilde J, Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML, Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G, Trials & Registries Subcommittee, Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D, Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon J-L, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S, ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document Reviewers, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, et al. Third universal definition of myocardial infarction. *J. Am. Coll. Cardiol.* 2012; 60:1581–1598.

163. WHO | The top 10 causes of death [Internet]. WHO. [cited 2013 Jul 7];Available from: http://who.int/mediacentre/factsheets/fs310/en/

164. Puymirat E, Simon T, Steg PG, Schiele F, Guéret P, Blanchard D, Khalife K, Goldstein P, Cattan S, Vaur L, Cambou J-P, Ferrières J, Danchin N. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. *JAMA*. 2012; 308:998–1006.

165. Roger VL, Go AS, Lloyd-Jones DM, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Soliman EZ, Sorlie PD, Sotoodehnia N, Turan TN, Virani SS, Wong ND, Woo D, Turner MB, American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Executive summary: heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation*. 2012; 125:188–197.

166. Authors/Task Force Members, Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D, ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, Document Reviewers, Hasdai D, Astin F, Astrom-Olsson K, Budaj A, Clemmensen P, Collet J-P, Fox KA, Fuat A, Gustiene O, Hamm CW, Kala P, Lancellotti P, Maggioni AP, Merkely B, Neumann F-J, Piepoli MF, Van de Werf F, Verheugt F, Wallentin L. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). *European Heart Journal*. 2012; 33:2569–2619.

167. Mandelzweig L, Battler A, Boyko V, Bueno H, Danchin N, Filippatos G, Gitt A, Hasdai D, Hasin Y, Marrugat J, Van de Werf F, Wallentin L, Behar S, Euro Heart Survey Investigators. The second Euro Heart Survey on acute coronary syndromes: Characteristics, treatment, and outcome of patients with ACS in Europe and the Mediterranean Basin in 2004. *Eur. Heart J.* 2006; 27:2285–2293.

168. Fox KAA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA Jr, Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006; 333:1091.

169. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J. Am. Coll. Cardiol.* 2000; 35:569–582.

170. Korup E, Dalsgaard D, Nyvad O, Jensen TM, Toft E, Berning J. Comparison of degrees of left ventricular dilation within three hours and up to six days after onset of first acute myocardial infarction. *Am. J. Cardiol.* 1997; 80:449–453.

171. Weisman HF, Bush DE, Mannisi JA, Bulkley BH. Global cardiac remodeling after acute myocardial infarction: a study in the rat model. *J. Am. Coll. Cardiol.* 1985; 5:1355–1362.

172. Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. *Circulation*. 1991; 83:1849–1865.

173. Anversa P, Olivetti G, Capasso JM. Cellular basis of ventricular remodeling after myocardial infarction. *Am. J. Cardiol.* 1991; 68:7D–16D.

174. Segura AM, Frazier OH, Buja LM. Fibrosis and heart failure. *Heart Fail Rev*. 2012;

175. Zannad F, Rossignol P, Iraqi W. Extracellular matrix fibrotic markers in heart failure. *Heart Fail Rev*. 2010; 15:319–329.

176. Laurent GJ. Dynamic state of collagen: pathways of collagen degradation in vivo and their possible role in regulation of collagen mass. *Am. J. Physiol.* 1987; 252:C1–9.

177. Weber KT. Targeting pathological remodeling: concepts of cardioprotection and reparation. *Circulation*. 2000; 102:1342–1345.

178. Medugorac I, Jacob R. Characterisation of left ventricular collagen in the rat. *Cardiovasc. Res.* 1983; 17:15–21.

179. J. Lijnen P, Maharani T, Finahari N, S. Prihadi J. Serum Collagen Markers and Heart Failure. *Cardiovascular & Hematological Disorders-Drug Targets*. 2012; 12:51–55.

180. Klappacher G, Franzen P, Haab D, Mehrabi M, Binder M, Plesch K, Pacher R, Grimm M, Pribill I, Eichler HG. Measuring extracellular matrix turnover in the serum of patients with idiopathic or ischemic dilated cardiomyopathy and impact on diagnosis and prognosis. *Am. J. Cardiol.* 1995; 75:913–918.

181. Querejeta R, Varo N, López B, Larman M, Artiñano E, Etayo JC, Martínez Ubago JL, Gutierrez-Stampa M, Emparanza JI, Gil MJ, Monreal I, Mindán JP, Díez J. Serum carboxy-terminal propeptide of procollagen type I is a marker of myocardial fibrosis in hypertensive heart disease. *Circulation*. 2000; 101:1729–1735.

182. López B, Querejeta R, González A, Sánchez E, Larman M, Díez J. Effects of loop diuretics on myocardial fibrosis and collagen type I turnover in chronic heart failure. *J. Am. Coll. Cardiol.* 2004; 43:2028–2035.

183. Querejeta R, López B, González A, Sánchez E, Larman M, Martínez Ubago JL, Díez J. Increased collagen type I synthesis in patients with heart failure of hypertensive origin: relation to myocardial fibrosis. *Circulation*. 2004; 110:1263–1268.

184. López B, González A, Díez J. Circulating biomarkers of collagen metabolism in cardiac diseases. *Circulation*. 2010; 121:1645–1654.

185. Krum H, Elsik M, Schneider HG, Ptaszynska A, Black M, Carson PE, Komajda M, Massie BM, McKelvie RS, McMurray JJ, Zile MR, Anand IS. Relation of peripheral collagen markers to death and hospitalization in patients with heart failure and preserved

ejection fraction: results of the I-PRESERVE collagen substudy. *Circ Heart Fail*. 2011; 4:561–568.

186. Cicoira M, Rossi A, Bonapace S, Zanolla L, Golia G, Franceschini L, Caruso B, Marino PN, Zardini P. Independent and additional prognostic value of aminoterminal propeptide of type III procollagen circulating levels in patients with chronic heart failure. *J. Card. Fail.* 2004; 10:403–411.

187. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the randomized aldactone evaluation study (RALES). Rales Investigators. *Circulation*. 2000; 102:2700–2706.

188. Poulsen SH, Høst NB, Jensen SE, Egstrup K. Relationship between serum amino-terminal propeptide of type III procollagen and changes of left ventricular function after acute myocardial infarction. *Circulation*. 2000; 101:1527–1532.

189. Sato Y, Kataoka K, Matsumori A, Sasayama S, Yamada T, Ito H, Takatsu Y. Measuring serum aminoterminal type III procollagen peptide, 7S domain of type IV collagen, and cardiac troponin T in patients with idiopathic dilated cardiomyopathy and secondary cardiomyopathy. *Heart*. 1997; 78:505–508.

190. Manhenke C, Orn S, Squire I, Radauceanu A, Alla F, Zannad F, Dickstein K. The prognostic value of circulating markers of collagen turnover after acute myocardial infarction. *Int. J. Cardiol.* 2011; 150:277–282.

191. Kitahara T, Takeishi Y, Arimoto T, Niizeki T, Koyama Y, Sasaki T, Suzuki S, Nozaki N, Hirono O, Nitobe J, Watanabe T, Kubota I. Serum carboxy-terminal telopeptide of type I collagen (ICTP) predicts cardiac events in chronic heart failure patients with preserved left ventricular systolic function. *Circ. J.* 2007; 71:929–935.

192. Plaksej R, Kosmala W, Frantz S, Herrmann S, Niemann M, Störk S, Wachter R, Angermann CE, Ertl G, Bijnens B, Weidemann F. Relation of circulating markers of fibrosis and progression of left and right ventricular dysfunction in hypertensive patients with heart failure. *J. Hypertens.* 2009; 27:2483–2491.

193. López B, González A, Querejeta R, Larman M, Díez J. Alterations in the pattern of collagen deposition may contribute to the deterioration of systolic function in hypertensive patients with heart failure. *J. Am. Coll. Cardiol.* 2006; 48:89–96.

194. Risteli J, Risteli L. Analysing connective tissue metabolites in human serum. Biochemical, physiological and methodological aspects. *J. Hepatol.* 1995; 22:77–81.

195. Brilla CG, Weber KT. Reactive and reparative myocardial fibrosis in arterial hypertension in the rat. *Cardiovasc. Res.* 1992; 26:671–677.

196. Schaper J, Froede R, Hein S, Buck A, Hashizume H, Speiser B, Friedl A, Bleese N. Impairment of the myocardial ultrastructure and changes of the cytoskeleton in dilated cardiomyopathy. *Circulation*. 1991; 83:504–514.

197. Gandhi MS, Kamalov G, Shahbaz AU, Bhattacharya SK, Ahokas RA, Sun Y, Gerling IC, Weber KT. Cellular and molecular pathways to myocardial necrosis and replacement fibrosis. *Heart Fail Rev*. 2011; 16:23–34.

198. Spinale FG. Myocardial matrix remodeling and the matrix metalloproteinases: influence on cardiac form and function. *Physiol. Rev.* 2007; 87:1285–1342.

199. Bujak M, Frangogiannis NG. The role of TGF-beta signaling in myocardial infarction and cardiac remodeling. *Cardiovasc. Res.* 2007; 74:184–195.

200. Leask A. TGFbeta, cardiac fibroblasts, and the fibrotic response. *Cardiovasc. Res.* 2007; 74:207–212.

201. Anker SD, von Haehling S. Inflammatory mediators in chronic heart failure: an overview. *Heart*. 2004; 90:464–470.

202. Hedayat M, Mahmoudi MJ, Rose NR, Rezaei N. Proinflammatory cytokines in heart failure: double-edged swords. *Heart Fail Rev*. 2010; 15:543–562.

203. Schnee JM, Hsueh WA. Angiotensin II, adhesion, and cardiac fibrosis. *Cardiovasc. Res.* 2000; 46:264–268.

204. Iraqi W, Rossignol P, Angioi M, Fay R, Nuée J, Ketelslegers JM, Vincent J, Pitt B, Zannad F. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. *Circulation*. 2009; 119:2471–2479.

205. Mandry D, Eschalier R, Kearney-Schwartz A, Rossignol P, Joly L, Djaballah W, Böhme P, Escanyé JM, Vuissoz PA, Fay R, Zannad F, Marie PY. Comprehensive MRI analysis of early cardiac and vascular remodeling in middle-aged patients with abdominal obesity. *J. Hypertens.* 2012; 30:567–573.

206. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* 2011; 364:11–21.

207. Eschalier R, McMurray JJV, Swedberg K, van Veldhuisen DJ, Krum H, Pocock SJ, Shi H, Vincent J, Rossignol P, Zannad F, Pitt B. Safety and efficacy of eplerenone in patients at high-risk for hyperkalemia and/or worsening renal function: Analyses of EMPHASIS-HF study subgroups. *J. Am. Coll. Cardiol.* 2013;

208. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin. Pharmacol. Ther*. 2001; 69:89–95.

209. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. *Circulation*. 2006; 113:2335–2362.

210. Wagner JA. Biomarkers: principles, policies, and practice. *Clin. Pharmacol. Ther.* 2009; 86:3–7.

211. Delcayre C, Silvestre JS. Aldosterone and the heart: towards a physiological function? *Cardiovasc. Res.* 1999; 43:7–12.

212. Lijnen P, Petrov V. Antagonism of the renin-angiotensin-aldosterone system and collagen metabolism in cardiac fibroblasts. *Methods Find Exp Clin Pharmacol*. 1999; 21:215–227.

213. Janicki JS, Brower GL, Gardner JD, Chancey AL, Stewart JA Jr. The dynamic interaction between matrix metalloproteinase activity and adverse myocardial remodeling. *Heart Fail Rev*. 2004; 9:33–42.

214. Martos R, Baugh J, Ledwidge M, O'Loughlin C, Conlon C, Patle A, Donnelly SC, McDonald K. Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction. *Circulation*. 2007; 115:888–895.

215. Zhao H, Gu D, Jiao W, Huang Y, Liu P, Zhao L, Yu H. [Effects of spironolactone on type I, III collagen concentration in myocardium of spontaneous hypertension rats]. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2013; 42:81–85.

216. Li H, Simon H, Bocan TM, Peterson JT. MMP/TIMP expression in spontaneously hypertensive heart failure rats: the effect of ACE- and MMP-inhibition. *Cardiovasc. Res.* 2000; 46:298–306.

217. Pitt B, Reichek N, Willenbrock R, Zannad F, Phillips RA, Roniker B, Kleiman J, Krause S, Burns D, Williams GH. Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation*. 2003; 108:1831–1838.

218. Sato A, Takane H, Saruta T. High serum level of procollagen type III amino-terminal peptide contributes to the efficacy of spironolactone and angiotensin-converting enzyme inhibitor therapy on left ventricular hypertrophy in essential hypertensive patients. *Hypertens. Res.* 2001; 24:99–104.

219. Wright JW, Mizutani S, Harding JW. Pathways involved in the transition from hypertension to hypertrophy to heart failure. Treatment strategies. *Heart Fail Rev*. 2008; 13:367–375.

220. Quilliot D, Alla F, Böhme P, Bruntz J-F, Hammadi M, Dousset B, Ziegler O, Zannad F. Myocardial collagen turnover in normotensive obese patients: relation to insulin resistance. *Int J Obes (Lond)*. 2005; 29:1321–1328.

221. Stehr CB, Mellado R, Ocaranza MP, Carvajal CA, Mosso L, Becerra E, Solis M, García L, Lavandero S, Jalil J, Fardella CE. Increased levels of oxidative stress, subclinical inflammation, and myocardial fibrosis markers in primary aldosteronism patients. *J. Hypertens*. 2010; 28:2120–2126.

222. Habibi J, Demarco VG, Ma L, Pulakat L, Rainey WE, Whaley-Connell AT, Sowers JR. Mineralocorticoid receptor blockade improves diastolic function independent of blood pressure reduction in a transgenic model of RAAS overexpression. *Am. J. Physiol. Heart Circ. Physiol*. 2011; 300:H1484–1491.

223. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ*. 2009; 338:b1665.

224. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N. Engl. J. Med.* 2006; 355:251–259.

225. Paulus WJ, van Ballegoij JJM. Treatment of heart failure with normal ejection fraction: an inconvenient truth! *J. Am. Coll. Cardiol.* 2010; 55:526–537.

226. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur. Heart J.* 2011; 32:670–679.

227. Weber KT, Brilla CG, Janicki JS. Myocardial fibrosis: functional significance and regulatory factors. *Cardiovasc. Res.* 1993; 27:341–348.

228. Ahmed SH, Clark LL, Pennington WR, Webb CS, Bonnema DD, Leonardi AH, McClure CD, Spinale FG, Zile MR. Matrix metalloproteinases/tissue inhibitors of metalloproteinases: relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease. *Circulation*. 2006; 113:2089–2096.

229. Barasch E, Gottdiener JS, Aurigemma G, Kitzman DW, Han J, Kop WJ, Tracy RP. The relationship between serum markers of collagen turnover and cardiovascular outcome in the elderly: the Cardiovascular Health Study. *Circ Heart Fail*. 2011; 4:733–739.

230. Mak GJ, Ledwidge MT, Watson CJ, Phelan DM, Dawkins IR, Murphy NF, Patle AK, Baugh JA, McDonald KM. Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. *J. Am. Coll. Cardiol*. 2009; 54:1674–1682.

231. Cleland JGF, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J, PEP-CHF Investigators. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. *Eur. Heart J.* 2006; 27:2338–2345.

232. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJV, Michelson EL, Olofsson B, Ostergren J, CHARM Investigators and Committees. Effects of candesartan

in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003; 362:777–781.

233. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A, I-PRESERVE Investigators. Irbesartan in patients with heart failure and preserved ejection fraction. *N. Engl. J. Med.* 2008; 359:2456–2467.

234. Deswal A, Richardson P, Bozkurt B, Mann DL. Results of the Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction trial (RAAM-PEF). *J. Card. Fail.* 2011; 17:634–642.

235. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen H-D, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B, Aldo-DHF Investigators. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA*. 2013; 309:781–791.

236. Desai AS, Lewis EF, Li R, Solomon SD, Assmann SF, Boineau R, Clausell N, Diaz R, Fleg JL, Gordeev I, McKinlay S, O'Meara E, Shaburishvili T, Pitt B, Pfeffer MA. Rationale and design of the treatment of preserved cardiac function heart failure with an aldosterone antagonist trial: a randomized, controlled study of spironolactone in patients with symptomatic heart failure and preserved ejection fraction. *Am. Heart J.* 2011; 162:966–972.e10.

237. Beygui F, Collet J-P, Benoliel J-J, Vignolles N, Dumaine R, Barthélémy O, Montalescot G. High plasma aldosterone levels on admission are associated with death in patients presenting with acute ST-elevation myocardial infarction. *Circulation*. 2006; 114:2604–2610.

238. Beygui F, Vicaut E, Ecollan P, Machecourt J, Van Belle E, Zannad F, Montalescot G. Rationale for an early aldosterone blockade in acute myocardial infarction and design of the ALBATROSS trial. *Am. Heart J.* 2010; 160:642–648.

239. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, Oliveira A. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur. J. Heart Fail*. 2002; 4:531–539.

240. Komajda M, Hanon O, Hochadel M, Follath F, Swedberg K, Gitt A, Cleland JGF. Management of octogenarians hospitalized for heart failure in Euro Heart Failure Survey I. *Eur. Heart J*. 2007; 28:1310–1318.

241. Johnson D, Jin Y, Quan H, Cujec B. Beta-blockers and angiotensin-converting enzyme inhibitors/receptor blockers prescriptions after hospital discharge for heart failure are associated with decreased mortality in Alberta, Canada. *J. Am. Coll. Cardiol*. 2003; 42:1438–1445.

242. Eschalier R, Jean F, Pereira B, Monzy S, Vorilhon C, Mactoux V, Citron B, Sapin V, Motreff P, Lusson JR. Is there benefit in optimising heart failure treatment in over-80 year-old patients? (HF-80 study): study protocol for a randomized controlled trial. *Trials*. 2012; 13:25.

243. Chung ES, Leon AR, Tavazzi L, Sun J-P, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu C-M, Gorcsan J 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation*. 2008; 117:2608–2616.

244. Goldenberg I, Moss AJ, Hall WJ, Foster E, Goldberger JJ, Santucci P, Shinn T, Solomon S, Steinberg JS, Wilber D, Barsheshet A, McNitt S, Zareba W, Klein H. Predictors of response to cardiac resynchronization therapy in the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT). *Circulation*. 2011; 124:1527–1536.

245. Lopez-Andrès N, Rossignol P, Iraqi W, Fay R, Nuée J, Ghio S, Cleland JGF, Zannad F, Lacolley P. Association of galectin-3 and fibrosis markers with long-term cardiovascular outcomes in patients with heart failure, left ventricular dysfunction, and dyssynchrony: insights from the CARE-HF (Cardiac Resynchronization in Heart Failure) trial. *Eur. J. Heart Fail.* 2012; 14:74–81.

8 ANNEXE 1

Eschalier et al. Trials 2012, 13:25
http://www.trialsjournal.com/content/13/1/25

TRIALS

STUDY PROTOCOL Open Access

Is there benefit in optimising heart failure treatment in over-80 year-old patients? (HF-80 study): study protocol for a randomized controlled trial

Romain Eschalier[1,3,4*], Frédéric Jean[1], Bruno Pereira[2], Séverine Monzy[1], Charles Vorilhon[1], Valérie Mactoux[6], Bernard Citron[1,3], Vincent Sapin[3,5], Pascal Motreff[1,3,4] and Jean R Lusson[1,3,4]

Abstract

Background: An aging population and better management of various heart diseases explain the exponential growth in incidence and prevalence of chronic heart failure, with poor prognosis and heavy health costs. Medical management is codified in international guidelines. The management of heart failure in over-80 year-old patients follows these guidelines, but no clinical trials have been able to confirm benefit. Moreover, registries show down-prescription of heart failure treatments in the elderly and over-80s.

Methods/Design: We present the design of the HF-80 ("Is there benefit in optimising heart failure treatment in over-80 year-old patients?") study, which is a prospective randomised open-label clinical trial with blinded end-points, designed to evaluate the effect of optimising management by adhering to guidelines in over-80 year-old heart failure patients. Patients over 80 years of age admitted with acute heart failure will be included. The primary endpoint is to assess quality of life at 6 months on the Minnesota questionnaire. The secondary endpoints are to assess the effect of optimised management on quality of life, mortality, readmission for acute heart failure, cardiac fibrosis and economic data at 12 months. 80 patients will be included, divided into 2 groups: group A, with usual heart failure management by general practitioners; and group B, with optimised management based on international guidelines.

Discussion: It is necessary to assess the benefit of guidelines in over-80 year-old heart failure patients because of the fragility of this population and the elevated risk of iatrogenic complications.

Trial Registration: Clinical trials.gov number: NCT01437371.

Keywords: Heart failure, Aged and over 80, clinical trial, quality of life

Background

An aging population and improved management of various heart diseases involving ischemic aetiologies explain the growth in incidence and prevalence of chronic heart failure (HF) [1], with high complication rates [2,3] and heavy costs (more than 1% of total health care costs in industrialised countries). Mean age at diagnosis of HF was 70 years in the Framingham cohort [3]. Incidence and prevalence increase exponentially with age [3].

Angiotensin-converting enzyme inhibitors (ACEi) [4,5] beta-blockers [6,7], mineralocorticoid receptor antagonists [8], and angiotensin receptor blockers [9,10] provide first-line therapeutic management of HF as recommended in international guidelines [11,12]. These, however, are based on studies conducted on younger patients (mean age between 61 and 71 years: Table 1). Clinical management of over-80 year-old HF patients conforms to these guidelines, but no clinical trials have been able to confirm their benefit in this population. Comorbidity and iatrogenic complications may impair the effect of common treatments. Recent clinical trials

* Correspondence: reschalier@chu-clermontferrand.fr
[1]CHU Clermont-Ferrand, Service Cardiology, F-63000 Clermont-Ferrand
Full list of author information is available at the end of the article

Table 1 Mean age of main studies in HF management

Clinical studies	Ages of placebo Group (years old)	Ages of studied drug group (years old)
HF subgroup of Hyvet (hypertension study)	83.5 ± 3.1	83.6 ± 3.2
Seniors	76.1 ± 4.8	76.1 ± 4.8
Charm-Alternative	66.8 ± 10.5	66.3 ± 11
Merit HF	63.7	63.9
Charm-Added	64.1 ± 11.3	64.0 ± 10.7
Consensus		71
Solvd	59.1	59.1
Cibis II	61	61
Emphasis-HF	68.6 ± 7.6	68.7 ± 7.7
Ephesus	66 ± 12	64 ± 11
Rales	65 ± 12	65 ± 12
Atlas study	Low-dose of lisinopril: 63.6 ± 10.3	High-dose of lisinopril: 63.6 ± 10.5
Elite-1 trial	Losartan: 74(5-8)	Captopril: 73 (6-1)
Elite-II trial	Losartan: 71.4 (6-7)	Captopril: 71 (6-9)
Shift	60.1 ± 11.5	60.7 ± 11.2
Copernicus	63.4 ± 11.5	63.2 ± 11.4
Valiant	Captopril: 64.9 ± 11.8 Valsartan: 65 ± 11.8	Valsartan + Captopril: 64.6 ± 11.9
Dig	63.9 ± 11.7	63.8 ± 11

in HF management continued to recruit younger subjects, because of the need to highlight a beneficial effect of the treatment tested [13-15]. Some studies have reported benefit with such treatments in this kind of population [16,17]. Registries and observational studies highlighted down-prescription, especially for ACEi and beta-blockers, in elderly and over-80 year-old patients [18,19].

Methods/Design

Heart failure management is now clearly codified for the general population, thanks to several studies and guidelines. Management of over-80 year-old HF patients, however, is simply extrapolated from their findings. No study has specifically assessed optimised HF treatment in the over-80s, where potential benefit could be counterbalanced by co-morbidity and iatrogenic complications. The HF-80 clinical trial was designed as a pilot study to investigate whether optimised management has an effect on quality of life (QOL) in over-80 year-old HF patients.

The HF-80 Study

Objectives and endpoints

The primary objective of this pilot study is to assess optimised HF management, according to the guidelines of the European Society of Cardiology (ESC) [11,12], in terms of impact on QOL in over-80 year-old patients at 6 months.

The secondary objectives are to evaluate the effect of optimised management on:

- Quality of life at 12 months
- Mortality at 12 months
- Readmission for acute HF at 12 months
- Cardiovascular events at 12 months
- Cardiac fibrosis, evaluated by collagen peptides.

The primary assessment criterion is QOL at 6 months, assessed on the Minnesota Living with Heart Failure Questionnaire (LHFQ) [20].

The secondary assessment criteria are QOL at 12 months, measured by both the SF 12 [21] and LHFQ [20] (to check which scale is most suited to this population), mortality at 12 months, number of readmissions for acute HF, cardiovascular events at 12 months, evolution in New York Hospital Association (NYHA) class (at baseline, 6 months and 12 months), and evolution in 6-minutes walking test (6MWT) (at baseline, 6 months and 12 months). Finally, an analysis of the medical and economic interest of this support will be conducted.

This pilot study will also help lay the groundwork for a French national multicentre study of the management of octogenarian HF patients to find what support is most appropriate.

Study design

The HF-80 pilot study is a prospective randomised single-centre open-label clinical trial with blinded

Table 2 Inclusion and exclusion criteria in HF 80 study

Inclusion criteria:	
	Aged over-80 year-old subjects
	Hospitalized for an acute heart failure
	Left Ventricle Ejection Fraction ≤ 35%
	Evaluated life expectancy (Seattle Heart failure score) > 1 year
Exclusion criteria:	
	Dementia (evaluated by MMSE)
	Do not understand French language
	Followed with an optimized management
	With reduced mobility
	Recruited in another clinical trial or in a HF management network
	Acute HF with curable aetiology: cardiovascular surgery for coronary artery bypass graft or valvular replacement, angioplasty
	MDRD < 30 ml/min/1.73 m^2

endpoints. Current lack of knowledge regarding management for this population requires a pilot study, to harvest data before starting a clinical trial to assess mortality. The study population is over-80 year-old patients recently admitted for acute HF. Inclusion and exclusion criteria are listed in Table 2.

Dementia will be assessed by the Mini mental state examination (MMSE): patients with scores under 24/30 will not be included. For the very elderly, a preliminary walking test will be performed, to exclude patients with reduced mobility, who are moreover very often subject to dementia.

Randomisation

Included patients will be randomly allocated to either arm in a 1:1 ratio. The randomisation list is generated by minimisation [22] to maintain better balance than with traditional block randomisation. Stratification will be performed on gender (female/male), readmission (yes/no) and residence (at home/not at home). When a patient is considered eligible and informed consent has been obtained, randomisation will be performed automatically (on software) by an independent statistician.

Investigation Procedure

Over-80 year-old patients will be recruited and randomised into 2 groups of 40 (Figure 1):

- Group A: "usual care" management by the patient's usual general practitioner (GP) and cardiologist;
- Group B: "optimised" management strictly adhering to ESC guidelines [11,12], performed by the patient's usual GP and cardiologist plus day-hospital.

Patients will be included in HF-80 at discharge from acute HF care. Before inclusion, trans-thoracic echocardiography will confirm that left ventricle ejection fraction is under 35% and that no exclusion criteria are present. During hospital care, patients of both groups will receive the same treatments, so far as possible using all HF therapeutics; different hospital treatment according to group would not be ethically acceptable. Mean hospital stay is about 10 days, which is too short to induce bias, as medical management optimisation applies only after discharge. Optimised management will be assessed with long-term prognosis.

An identical assessment is to be performed at baseline and at 12 months for all patients (groups A and B) (Figure 2):

- Clinical examination: NYHA class; weight; height; heart rate; blood pressure; right, left or both HF symptoms; triggering factor; cardiovascular risk factors; thyroid pathologies; personal cardiovascular history;
- Quality of life questionnaires (LHFQ [20], SF 12 [21]);
- Six-minutes walking test (6MWT);
- Electrocardiogram (EKG);
- Transthoracic echocardiography (TTE);
- Blood test (haemoglobin, kaliaemia, natraemia, liver assessment, bilirubin, Modification in Diet

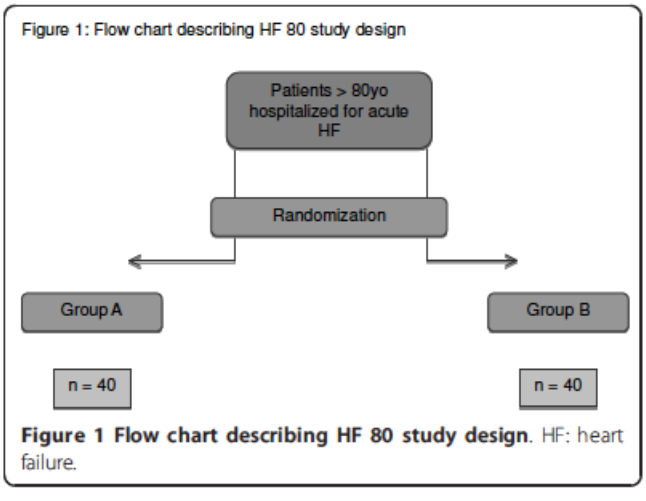


Figure 1 Flow chart describing HF 80 study design. HF: heart failure.

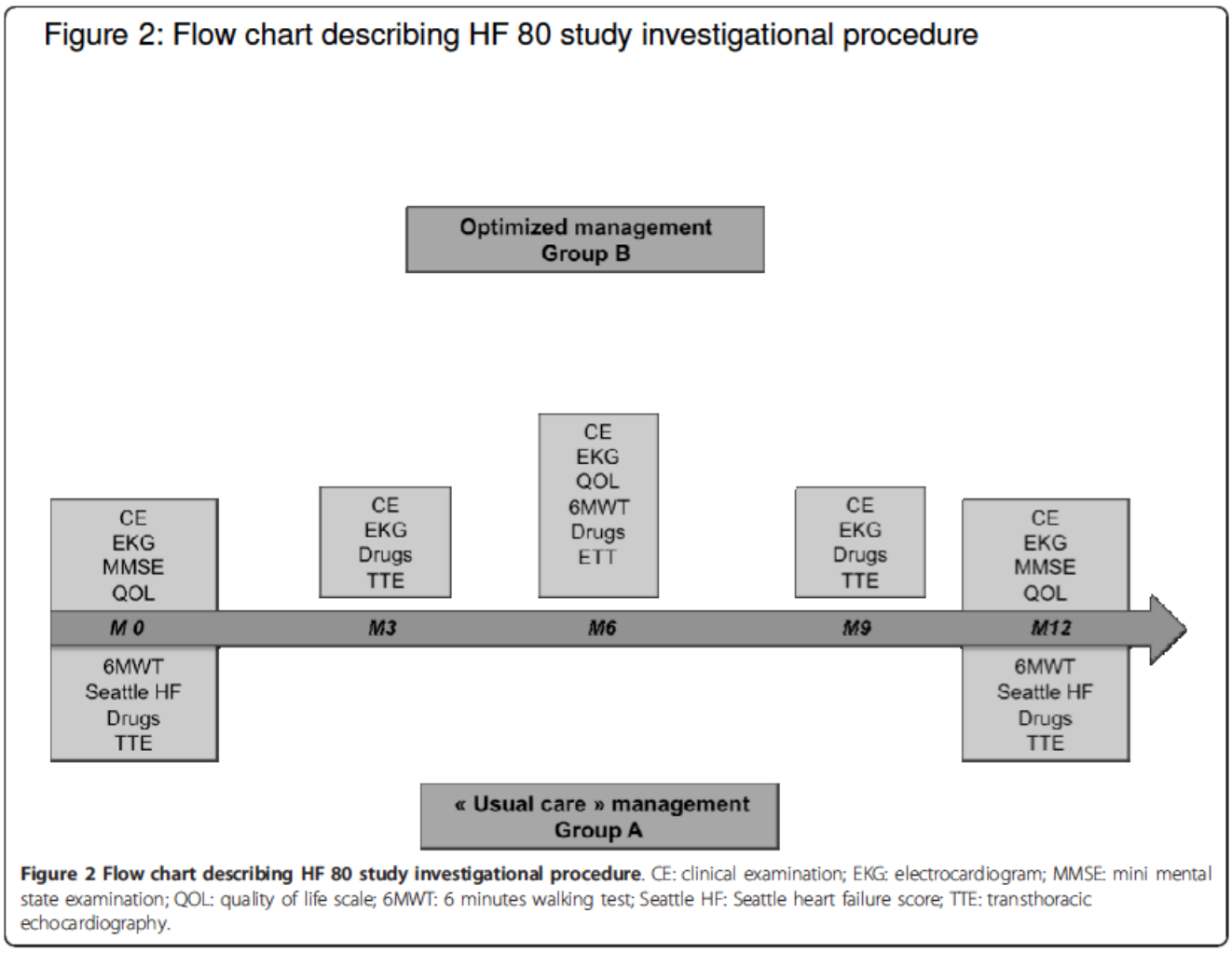


Figure 2 Flow chart describing HF 80 study investigational procedure. CE: clinical examination; EKG: electrocardiogram; MMSE: mini mental state examination; QOL: quality of life scale; 6MWT: 6 minutes walking test; Seattle HF: Seattle heart failure score; TTE: transthoracic echocardiography.

Renal Disease (MDRD) [23], N-Terminal of pro-Brain Natriuretic Peptide (NT-pro-BNP), and nutritional tests (C-reactive protein, albumin, prealbumin and orosomucoid);

- Renin, aldosterone and collagen peptides [type 1 collagen telopeptide (ICTP), aminoterminal propeptide of type I procollagen (PINP), aminoterminal propeptide of type III procollagen (PIIINP)], and galectin 3;
- Mini mental state examination (MMSE) [24].

During primary hospital care for acute HF and at discharge, both groups will have the same management with initiation of the same treatments, following guidelines [11,12].

Group A subjects will be followed up by their usual GP and cardiologist without any day-hospital care ("usual care" management). The GP and cardiologist will manage treatment optimisation as they are used to doing.

Group B subjects will have the same management as group A but will also receive day-hospital care. The first 3 visits will be at 3 weekly intervals, except in case of unstable HF, and then every 6 weeks for 12 months, to optimise treatment.

During each day-hospital visit in group B, certain data will be recorded to optimise HF management:

- Clinical examination (NYHA class, HF symptoms, blood pressure, heart rate);
- Blood sample (kaliaemia, MDRD [23], NT-pro-BNP);
- Electrocardiogram;
- Optimised treatment doses, if possible, for ACEi, beta-blockers, angiotensin receptor blocker and mineralocorticoid receptor antagonist.

All the visits and contents are described in Table 3.

Patients in both groups will have a notebook, for 12 months. GPs and cardiologists will note all changes in treatment and management.

Table 3 Schedule of visits and contents

	Group A		Group B					
	Enrollement hospitalization	*Month 12 visit*	*Enrollement hospitalization*	*Day hospital visits*	*Month 3 visit*	*Month 6 visit*	*Month 9 visit*	*Month 12 visit*
QOL questionnaires (LVHQ, SF12)	X	X	X			X		X
Clinical examination (BP, HR, weight, NYHA)	X	X	X	X	X		X	X
EKG	X	X	X	X	X	X	X	X
6MWT	X	X	X					X
Na, Hb, SGOT, SGPT, Bili	X	X	X					X
K, MDRD, NT-pro-BNP	X	X	X	X	X	X	X	X
PCR, oroso, alb, prealb	X	X	X					X
TTE	X	X	X		X	X	X	X
Blood laboratory	X	X	X		X	X	X	X
Treatments	X	X	X	X	X	X	X	X

BP: blood pressure; HR: heart rate; EKG: electrocardiogram; MMSE: mini mental state examination; QOL: quality of life; 6MWT: 6 minutes walking test; Seattle HF: Seattle heart failure score; TTE: transthoracic echocardiography; CRP: C reactive protein; oroso: orosomucoid; alb: albumin; prealb: prealbumin; MDRD: Modification in Diet Renal Disease; NT-ProBNP: N terminal pro brain natriuretic peptid; K: kaliemia; Na: sodium blood concentration; Hb: hemoglobin; bili: biliubin; SGPT: Serum Glutamopyruvate Transferase, SGOT: Serum Glutamooxaloacetate Transferase.

Transthoracic echocardiography analysis

TTE will be performed using a 2.5 MHz probe (VIVID 9, General Electrics), by a single operator [25], at inclusion and at 12 months, in both groups. TTE will also be performed at 3, 6 and 9 months for group B in day hospital, and according to "usual management" criteria for group A.

The following measurements will be taken in each subject:

2D/MM modes: Right ventricle (RV) diameter (mm); interventricular septum thickness at end diastole and end systole (mm); left ventricle (LV) posterior wall thickness at end diastole and end systole (mm); LV diameter at end diastole and end systole (mm); LV volumes at end diastole and end systole (ml); LV ejection fraction measured by the biplane Simpson method (%); LV mass index (g/m2); inferior vena cava diameter (mm); left and right atrium areas (cm^2); RV volume; RV ejection fraction; TEI myocardial performance index; and tricuspid annular plane systolic excursion (TAPSE).

Doppler modes: transmitral flow, including peak E wave (cm/s), peak A wave (cm/s), E/A ratio, E-wave deceleration time (m/s); pulmonary venous waveforms, including peak systolic (S) velocity, peak anterograde diastolic (D) velocity, and S/D ratio; VP, Color M-Mode flow propagation velocity; relaxation isovolumic time (m/s); cardiac output, tricuspid E wave; tricuspid regurgitation (none/mean/moderate/severe); systolic pulmonary arterial pressure; mitral regurgitation (none/mean/moderate/severe); and dp/dt for left and right ventricle.

Doppler tissue imaging mode: lateral and septal E' wave and A wave at mitral annulus (cm/s), lateral and septal S wave at mitral annulus (cm/s); S' and E' wave at tricuspid annulus (cm/s).

2D-Strain mode: Loops obtained by 2D on 3 cycles, with apical 4-cavities, 3-cavities, 2-cavities and parasternal short axis views, with frame rate > 60 frames/s.

6-minutes walking test

This will be performed for each patient at inclusion and at 12 months, and also at 6 months for group B [26]. The test will be made in hospital on a 60-metre track. The patients will be requested to walk at their tolerance threshold for 6 minutes. Before the beginning of each test, respiratory frequency, heart rate, blood pressure and effort perception on the Borg scale [27,28] will be measured. At the end of each test, the same parameters will be measured again. The final result of the 6MWT is the total distance covered (metres) in 6 minutes.

Blood tests

The usual blood tests made during acute HF hospitalisation will be performed by the hospital biochemistry laboratory: haemoglobin, K, Na, liver assessment, bilirubin, MDRD [23], NT-pro-BNP, natriuresis, and nutritional tests (C-reactive protein, albumin, prealbumin and orosomucoid), using the AutomateVista 1500 (Siemens HealthCare Diagnostics)]. Renin (Liaison Direct Renin kit, Diasorin), aldosterone (ELISA Kit (E90911Hu), USC N Life Science Inc.), PIIINP (ELISA Kit (E90573Hu), USC N Life Science Inc.), PINP (ELISA Kit (E90957Hu), USC N Life Science Inc.), ICTP (ELISA Kit (E90665Hu), USC N Life Science Inc.) and galectin 3 (ELISA kit (DGAL30), R and D systems) will be analysed at end of trial, after storage at -80°C.

QOL scales

It was decided to implement two QOL questionnaires (LHFQ [20] and SF 12[21]) to assess which is more adapted to over-80 year-old HF patients. Both are well-validated and widely used. The SF12 is used on a daily basis in the geriatric department of our hospital and maybe more adapted to the elderly. A second endpoint is to assess the efficiency of this shorter QOL questionnaire, SF12, as compared to the LHFQ, in a very elderly population. They will be completed at inclusion and at 12 month for each subject. QOL scales will be sent to all participants (group A and B) at 6 months (before the 6 month visit for group B) and will be filled in by the patients without any help from medics or paramedics (to avoid bias).

Statistical Considerations

Due to lack of information in the literature concerning the management of over-80 year-old HF patients, it is difficult to estimate correct sample size. The number of subjects to be included is extrapolated from data obtained on younger patients, according to which 40 subjects per group will be included.

With a 2-tailed significance threshold of 0.05, statistical power of 90% and allowing for 15% loss to follow-up, 80 patients will be needed to show a difference of 20 points ($\sigma = 25$) in quality of life (LHFQ) at 6 months between the 2 randomisation arms [29]. Morcillo et al. demonstrated that a 20-point difference in LFHQ is significant and feasible in such a population at 6 months' follow-up. An interim analysis is planned. For 34 evaluable patients (17 per group), a difference in QOL score between the 2 arms will be considered significant for an adjusted α equal to 0.003 (Lan and DeMets, EaSt© software). Termination for futility can thus be considered.

The number of patients included and the curve of the inclusions, the theoretical number of visits for the number of patients included, the number of visits actually made and the ratio will be presented for the 2 groups. The cumulative duration of follow-up and the "total follow-up/expected cumulative follow-up" ratio will be calculated.

All analyses will be performed on an intention-to-treat basis. Clinically relevant baseline variables and primary and secondary endpoints will be compared between groups by Chi^2 or Fisher-exact tests (categorical variables) and by Student's t tests or Mann-Whitney tests as appropriate (continuous variables). Multivariate analyses to control for confounding effects of variables will be performed.

The survival analysis will be conducted in univariate analysis by log-rank test to compare survival curves following Kaplan-Meier, and in multivariate analysis by the Cox proportional regression model.

To measure the evolution of parameters over time points (visits), longitudinal data analysis will be conducted by ANOVA for repeated measures followed by Tukey-Kramer post-hoc test and by random effects models to measure within-subject correlation taking account of effects over time (random intercept and slope). The impact of covariates, such as randomisation group, will be explored to assess the impact of strategies on QOL score.

Treatment compliance will be analysed initially in a descriptive step and, if necessary, included in multivariate analysis.

A 2-tailed p value of 0.05 will be considered statistically significant (except in interim analysis). All analyses will be performed by STATAv11 (StataCorp, College Station, Texas, USA).

Discussion

The aging of the population [1] is increasing hospital admission for acute HF, particularly in subjects over 80 years of age. This is a special population, often with multiple comorbidity and a high risk of iatrogenic complications, in whom it is difficult to implement all recommended treatments at optimal doses. There is a significant difference between the optimal treatment doses according to the literature on HF and the doses actually prescribed to inpatients [18,19,30]. Guidelines are extrapolated to this population without knowing whether there is benefit.

Unfortunately, clinical trials on HF have recruited young patients. Clinical studies in cardiology, and particularly in HF, recruit young subjects at the expense of seniors who are underrepresented if not excluded [31-33]. This trend was confirmed by recent large studies of therapeutic drugs (Emphasis-HF [13] and SHIFT [14] subjects were aged, respectively, 68 and 60 years) and electric therapy [15]. The SENIORS study [17] confirmed the value of beta-blockers in patients over 70 years old; benefit, however, was especially pronounced in patients younger than 75 years. The ELITE study [34] was probably the first large HF trial to decide to exclude young patients: only over-65 year-olds were recruited, two-thirds aged 70 or older; the safety of losartan and captopril in HF was demonstrated. These findings were confirmed in morbidity and mortality, but in a younger population (over-60 year-old HF patients [35]. HYVET [16], an antihypertensive clinical trial, included patients over 80 years of age and showed benefit with medical treatment in hypertension in this age group, including in the subgroup with onset of HF (64% reduction). Observational studies and registries show down-prescription of recommended treatments, including ACEi and beta-blockers, in over-80 year-old HF patients [18,19,30].

This requires specific studies in elderly patients (> 80 years old) to consider the respective interest of different classes and recommended therapeutic doses. Given the aging population and the exponential prevalence of over-80 year-old HF patients, it is primordial to know if optimised management with increased treatment doses shows benefit in this population. Iatrogenic complications such as chronic renal failure, orthostatic hypotension or hyperkaliemia could aggravate clinical status in this population and counterbalance expected benefit. The ATLAS study confirmed that intermediate and high-dose lisinopril was more effective in terms of death and hospital admission than low doses, but with side effects (dizziness, hypotension, worsening renal function, hyperkaliaemia), although not such as to lead to termination of lisinopril [36].

A potential bias is present in this design. Patients in the "optimised" group will have more cardiology day-hospital visits; GPs will be in charge of their own management optimisation, as recommended in the ESC guidelines.

Divergent data are present in the literature on elderly HF patients, and there is no consensus on managing over-80 year-old patients. The growing size of this population requires clinical trials to confirm that the HF management validated in younger subjects is also effective in those over 80 years of age.

Trial Status

HF-80 study is in an activating recruiting phase since October 2011. Institute's committee on human research (CPP Sud Est VI) agreement was obtained in April 2011. Subjects will give their informed consent before being enrolled in the study. AFFSAPS agreement was obtained in May 2011. HF-80 will start enrolling patients in October 2011. Study completion date is estimated at December 2012. Clinical trials.gov number: NCT 01437371.

List of abbreviations

HF: Heart Failure; QOL: Quality of life; LVHQ: Minnesota living with heart failure questionnaire; LV: Left ventricle; 6MWT: 6 minutes walking test; TTE: transthoracic echocardiography; ESC: European society of cardiology; ACEi: angiotensin conversing enzyme inhibitors; NYHA: New York Heart Association; GP: general practitioner.

Acknowledgements

We thank Mr. Iain McGill for editing the manuscript and Mrs Valérie Batel for daily coordinating the HF80 clinical trial.

Author details

[1]CHU Clermont-Ferrand, Service Cardiology, F-63000 Clermont-Ferrand. [2]CHU Clermont-Ferrand, Clinical research and innovation direction, F-63000 Clermont-Ferrand. [3]University of Auvergne, F-6300 Clermont-Ferrand. [4]Clermont Université, Université d'Auvergne, UMR6284, F-63000 Clermont-Ferrand. [5]CHU Clermont-Ferrand, Service Biochimy, F-63000 Clermont-Ferrand. [6]CHU Clermont-Ferrand, Service Geriatric, F-63000 Clermont-Ferrand.

Authors' contributions

RE, FJ, SM, BP, and CV participated in the design of the study. RE and FJ participated in writing the manuscript. BP performed statistical section. VS participated in the biological part of the study. PM, JRL, BC helped to draft the manuscript, and participated in study design and coordination. All authors read and approved the final manuscript.

Competing interests

This clinical trial is funded by the support of Laboratoires Servier and Sorin group.
The authors declare that they have no competing interests and no other source of fundings than those cited above.

Received: 7 October 2011 Accepted: 6 March 2012
Published: 6 March 2012

References

1. Cowie MR, Wood DA, Coats AJ, Thompson SG, Poole-Wilson PA, Suresh V, Sutton GC: **Incidence and aetiology of heart failure; a population-based study.** *Eur Heart J* 1999, **20**:421-428.
2. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, Oliveira A: **Prevalence of chronic heart failure in Southwestern Europe: the EPICA study.** *Eur J Heart Fail* 2002, **4**:531-539.
3. Ho KK, Pinsky JL, Kannel WB, Levy D: **The epidemiology of heart failure: the Framingham Study.** *J Am Coll Cardiol* 1993, **22**:6A-13A.
4. Effects of enalapril on mortality in severe congestive heart failure: **Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group.** *N Engl J Med* 1987, **316**:1429-1435.
5. **Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigattors.** *N Engl J Med* 1992, **327**:685-691.
6. **The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial.** *Lancet* 1999, **353**:9-13.
7. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vítovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P: **Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group.** *JAMA* 2000, **283**:1295-1302.
8. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J: **The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators.** *N Engl J Med* 1999, **341**:709-717.
9. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K: **Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial.** *Lancet* 2003, **362**:772-776.
10. McMurray JJV, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA: **Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial.** *Lancet* 2003, **362**:767-771.
11. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJV, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K, Vahanian A, Camm J, De Caterina R, Dean V, Dickstein K, Filippatos G, Funck-Brentano C, Hellemans I, Kristensen SD, McGregor K, Sechtem U, Silber S, Tendera M, Widimsky P, Zamorano JL, Tendera M, Auricchio A, Bax J, Böhm M, Corrà U, Della Bella P, Elliott PM, Follath F, Gheorghiade M, Hasin Y, Hernborg A, Jaarsma T, Komajda M, Kornowski R, Piepoli M, Prendergast B, Tavazzi L, Vachiery J-L, Verheugt FWA, Zamorano JL, Zannad F: **ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM).** *Eur Heart J* 2008, **29**:2388-2442.

12. Dickstein K, Vardas PE, Auricchio A, Daubert J-C, Linde C, McMurray J, Ponikowski P, Priori SG, Sutton R, van Veldhuisen DJ, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Simes PA, Tendera M, Vardas P, Widimsky P, Tendera M, Anker SD, Blanc J-J, Gasparini M, Hoes AW, Israel CW, Kalarus Z, Merkely B, Swedberg K, Camm AJ: **2010 Focused Update of ESC Guidelines on device therapy in heart failure: an update of the 2008 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure and the 2007 ESC guidelines for cardiac and resynchronization therapy. Developed with the special contribution of the Heart Failure Association and the European Heart Rhythm Association.** *Eur Heart J* 2010, **31**:2677-2687.
13. Zannad F, McMurray JJV, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B: **Eplerenone in patients with systolic heart failure and mild symptoms.** *N Engl J Med* 2011, **364**:11-21.
14. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L: **Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study.** *The Lancet* 2010, **376**:875-885.
15. Salukhe TV, Francis DP, Sutton R: **Comparison of medical therapy, pacing and defibrillation in heart failure (COMPANION) trial terminated early; combined biventricular pacemaker-defibrillators reduce all-cause mortality and hospitalization.** *Int J Cardiol* 2003, **87**:119-120.
16. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ: **Treatment of hypertension in patients 80 years of age or older.** *N Engl J Med* 2008, **358**:1887-1898.
17. Flather MD, Shibata MC, Coats AJS, Van Veldhuisen DJ, Parkhomenko A, Borbola J, Cohen-Solal A, Dumitrascu D, Ferrari R, Lechat P, Soler-Soler J, Tavazzi L, Spinarova L, Toman J, Böhm M, Anker SD, Thompson SG, Poole-Wilson PA: **Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS).** *Eur Heart J* 2005, **26**:215-225.
18. Komajda M, Hanon O, Hochadel M, Follath F, Swedberg K, Gitt A, Cleland JGF: **Management of octogenarians hospitalized for heart failure in Euro Heart Failure Survey I.** *Eur Heart J* 2007, **28**:1310-1318.
19. Johnson D, Jin Y, Quan H, Cujec B: **Beta-blockers and angiotensin-converting enzyme inhibitors/receptor blockers prescriptions after hospital discharge for heart failure are associated with decreased mortality in Alberta, Canada.** *J Am Coll Cardiol* 2003, **42**:1438-1445.
20. Guyatt GH: **Measurement of health-related quality of life in heart failure.** *J Am Coll Cardiol* 1993, **22**:185A-191A.
21. Franzén K, Blomqvist K, Saveman B-I: **Impact of chronic heart failure on elderly persons' daily life: a validation study.** *Eur J Cardiovasc Nurs* 2006, **5**:137-145.
22. Signorini DF, Leung O, Simes RJ, Beller E, Gebski VJ, Callaghan T: **Dynamic balanced randomization for clinical trials.** *Stat Med* 1993, **12**:2343-2350.
23. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: **A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group.** *Ann Intern Med* 1999, **130**:461-470.
24. Folstein MF, Folstein SE, McHugh PR: **« Mini-mental state ». A practical method for grading the cognitive state of patients for the clinician.** *J Psychiatr Res* 1975, **12**:189-198.
25. Roelandt J, Gibson DG: **Recommendations for standardization of measurements from M-mode echocardiograms.** *Eur Heart J* 1980, **1**:375-378.
26. **ATS statement: guidelines for the six-minute walk test.** *Am J Respir Crit Care Med* 2002, **166**:111-117.
27. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL: **Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial.** *JAMA* 2009, **301**:1439-1450.
28. Fleg JL, Piña IL, Balady GJ, Chaitman BR, Fletcher B, Lavie C, Limacher MC, Stein RA, Williams M, Bazzarre T: **Assessment of functional capacity in clinical and research applications: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association.** *Circulation* 2000, **102**:1591-1597.
29. Morcillo C, Aguado O, Delás J, Rosell F: **[Utility of the Minnesota Living With Heart Failure Questionnaire for assessing quality of life in heart failure patients].** *Rev Esp Cardiol* 2007, **60**:1093-1096.
30. Komajda M, Hanon O, Hochadel M, Lopez-Sendon JL, Follath F, Ponikowski P, Harjola V-P, Drexler H, Dickstein K, Tavazzi L, Nieminen M: **Contemporary management of octogenarians hospitalized for heart failure in Europe: Euro Heart Failure Survey II.** *Eur Heart J* 2009, **30**:478-486.
31. Gurwitz JH, Col NF, Avorn J: **The exclusion of the elderly and women from clinical trials in acute myocardial infarction.** *JAMA* 1992, **268**:1417-1422.
32. Cherubini A, Oristrell J, Pla X, Ruggiero C, Ferretti R, Diestre G, Clarfield AM, Crome P, Hertogh C, Lesauskaite V, Prada G-I, Szczerbinska K, Topinkova E, Sinclair-Cohen J, Edbrooke D, Mills GH: **The persistent exclusion of older patients from ongoing clinical trials regarding heart failure.** *Arch Intern Med* 2011, **171**:550-556.
33. Gurwitz JH, Goldberg RJ: **Age-Based Exclusions From Cardiovascular Clinical Trials: Implications for Elderly Individuals (and for All of Us): Comment on « The Persistent Exclusion of Older Patients From Ongoing Clinical Trials Regarding Heart Failure ».** *Arch Intern Med* 2011, **171**:557-558.
34. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB, Chang PI: **Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE).** *Lancet* 1997, **349**:747-752.
35. Konstam MA, Neaton JD, Poole-Wilson PA, Pitt B, Segal R, Sharma D, Dasbach EJ, Carides GW, Dickstein K, Riegger G, Camm AJ, Martinez FA, Bradstreet DC, Ikeda LS, Santoro EP: **Comparison of losartan and captopril on heart failure-related outcomes and symptoms from the losartan heart failure survival study (ELITE II).** *Am Heart J* 2005, **150**:123-131.
36. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JGF, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF: **Comparative Effects of Low and High Doses of the Angiotensin-Converting Enzyme Inhibitor, Lisinopril, on Morbidity and Mortality in Chronic Heart Failure.** *Circulation* 1999, **100**:2312-2318.

doi:10.1186/1745-6215-13-25
Cite this article as: Eschalier *et al.*: Is there benefit in optimising heart failure treatment in over-80 year-old patients? (HF-80 study): study protocol for a randomized controlled trial. *Trials* 2012 **13**:25.

UNIVERSITE D'AUVERGNE

ECOLE DOCTORALE SCIENCES DE LA VIE ET DE LA SANTE DE L'AGRONOMIE ET DE L'ENVIRONNEMENT

THESE pour l'obtention du **DOCTORAT de l'Université d'Auvergne**

Soutenance publique le 04 Octobre 2013

Par Romain ESCHALIER

RESUME

Ce travail de thèse avait pour objectif d'évaluer l'intérêt des peptides collagéniques sanguins dans différentes populations à haut risque de développer une insuffisance cardiaque (patients présentant une obésité abdominale ou en post-infarctus du myocarde) ou déjà symptomatiques (post-infarctus du myocarde). En effet la fibrose myocardique est un élément essentiel de l'évolution péjorative de l'insuffisance cardiaque.

Ces travaux ont permis de montrer la pertinence clinique des dosages sanguins des peptides collagéniques tout au long du processus de l'insuffisance cardiaque : du stade asymptomatique aux stades symptomatiques. Nous avons mis en évidence, à travers l'expression des peptides collagéniques que :

1/ des patients asymptomatiques ayant une obésité abdominale présentent un remodelage cardiaque précoce tant structurel que fonctionnel (augmentation de la masse ventriculaire gauche, dysfonction diastolique associée au PIIINP) : R2C2 Study.

2/ le ratio PIIINP/ICTP ≤ 1, mesuré 1 mois après un infarctus, est indépendamment associé à la survenue d'un remodelage ventriculaire gauche à un an et améliore la prédiction de survenue d'évènements cardiovasculaires (décès cardiovasculaires et hospitalisation pour décompensation cardiaque) à 3 ans : REVE-2 study.

3/ les antagonistes des récepteurs aux minéralocorticoïdes (éplérénone), traitement anti-fibrotique par excellence, sont efficaces et sûrs (hyperkaliémie et insuffisance rénale) chez des patients à haut risque de remodelage et de complications: EMPHASIS-HF study.

Ce travail doit conduire à la validation dans d'autres populations du rôle prépondérant de la fibrose mais surtout au bénéfice thérapeutique des classes anti-fibrotiques dans l'insuffisance cardiaque.